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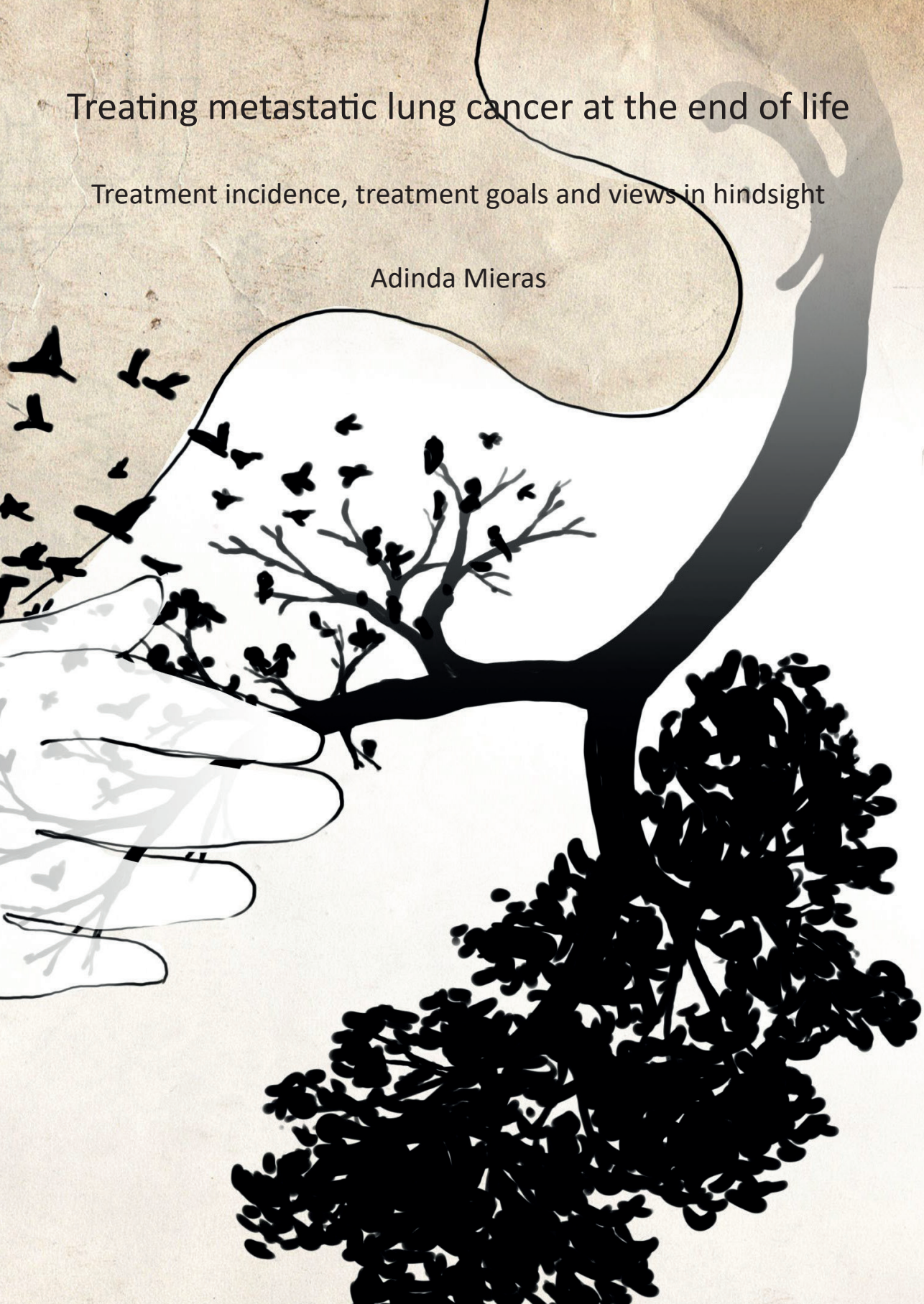

Treating metastatic lung cancer at the end of life

Treatment incidence, treatment goals and views in hindsight

by Adinda Mieras

The research described in this thesis was conducted at Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Pulmonary disease and Department of Public and Occupational Health, Amsterdam Public Health research institute, Expertise center for Palliative Care, Cancer Center Amsterdam, Amsterdam, the Netherlands

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dr. H.R.W. Pasman

Angst is een slechte raadgever

Fear is a poor basis for decision making

TABLE OF CONTENTS

1

GENERAL INTRODUCTION AND OUTLINE

The focus of this thesis is on patients with metastatic lung cancer who received a systemic treatment prior to the end of their life. This topic is studied from different perspectives and with different methodologies. Firstly, we looked into what percentage of metastatic lung cancer patients actually receive a systemic treatment prior to the end of life. Secondly, we studied the goals patients and their oncologists have when starting a treatment for metastatic lung cancer, we evaluated the achievement of these goals and the satisfaction with the treatment decision according to the patients, their oncologists and their relatives in hindsight.

Epidemiology of lung cancer

Lung cancer is currently one of the most frequently diagnosed cancers worldwide, accounting for about 20% of all cancer-related deaths.[1-3] According to the Netherlands Cancer Registry (Integraal Kankercentrum Nederland)[4], over 13,000 patients are diagnosed with lung cancer in the Netherlands every year, with a yearly mortality of over 10,000 patients.[5] This disease is associated with a high symptom burden, a low quality of life and an average five-year survival rate of 19%.[6-10] Factors contributing to this poor survival rate are comorbid conditions such as heart failure or chronic obstructive pulmonary disease and the fact that lung cancer is often diagnosed at an advanced stage.[11]

Lung cancer is classified into several histological subtypes, with approximately 80% of all lung cancer cases classified as non-small cell lung cancer (NSCLC) and 15% classified as small cell lung cancer (SCLC). The remaining cases comprises of a heterogeneous group of thoracic cancer (e.g. mesothelioma). NSCLC is further classified into adenocarcinoma, squamous cell carcinoma or large cell carcinoma.[12] The five-year survival rate of patients with NSCLC is 24%, while patients diagnosed with SCLC have an even worse survival rate of 6%.[10] Roughly half of the patients presenting with NSCLC have metastasized disease, also known as stage IV and for these patients the five-year survival rate is only 7% for NSCLC and 3% for SCLC.[13]

Systemic treatment of metastatic lung cancer

Systemic treatment is the use of medication to destroy cancer cells. This type of medication is given through the bloodstream to reach cancer cells throughout the body.[14] According to the guidelines from the European Society for Medical Oncology (ESMO), systemic therapy should be offered to all metastatic lung cancer patients who have a relatively good performance score (ECOG score of 0-2 (Eastern Cooperative Oncology Group)).[15] Additionally, every treatment strategy should take the following factors into account: histology and molecular pathology of the tumour, patient's age and comorbidities and the patient's preferences. In 1995, chemotherapy was established as a valuable systemic treatment for lung cancer when the NSCLC collaborative group published a meta-analysis of all randomized NSCLC clinical trials performed between 1982-2001. This data showed that treatment with chemotherapy, using mainly cisplatin-based regimens, leads to an absolute survival benefit of 10% at 1 year compared to best supportive care.[16] Later studies showed that the response rate of first

line chemotherapy is around 30% with a median duration of response between 3.5 and 5.5 months.[17] Unfortunately, the disadvantages of chemotherapy treatment are the well-known adverse events like vomiting, nausea, myelosuppression and alopecia, which vary in severity depending on the different chemotherapy regimens and the individual patient characteristics such as age and comorbidities.[18-20]

In the past decade, research on molecular targeted therapy has led to significant clinical improvements in various subsets of patients with NSCLC. In particular, Tyrosine Kinase Inhibitors (TKIs) act against specific targets, as opposed to classical cytotoxic chemotherapeutic drugs that damage all proliferating cells in a nonspecific manner. TKIs are small molecules that can easily enter cells and inhibit intracellular tyrosine kinase enzymes, deactivating signal transduction cascades resulting in the slowing down of tumour growth. For lung cancer, clinical practices worldwide use TKIs directed towards Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK) and mutations in the BRAF gene.[21] Patients harbouring a certain mutation, which is about 10% of the patients diagnosed with lung cancer, respond much better (a response rate of around 70%) and longer (up to 10 months) to TKIs than to chemotherapy.[22-26] However, TKIs are unfortunately also associated with adverse side effects such as skin problems, chronic diarrhea, fatigue and electrolyte imbalances.[27-29]

Another more recent promising systemic cancer therapy is immunotherapy using Monoclonal AntiBodies (MABs), which are large molecules that usually do not enter cells but primarily bind to extracellular targets such as cell surface proteins. In the Netherlands, immunotherapy treatment has been introduced for second line therapy after chemotherapy use since 2016.[30] Currently, for patients with metastatic NSCLC and a PD-L1 expression above 50%, monotherapy with immunotherapy is considered standard first-line treatment. For patients with a PD-L1 expression below 50% the new standard therapy is a combination of chemotherapy and immunotherapy.[31-33] In both cases this is only an option when they do not otherwise have contraindications to use of immunotherapy (such as severe autoimmune disease or organ transplantation) and have a wild type EGFR and ALK.[15] On average, 20% of lung cancer patients respond to immunotherapy with a prolonged median survival of 9 to 15 months.[34] Similar to other cancer therapies, there are several side effects associated with immunotherapy, including immune related events in different organ systems like the skin, gastro-intestinal tract, endocrine system and urinary system.[35]

Treatment in the context of the end of life

Previous studies have shown that the percentage of metastatic lung cancer patients receiving chemotherapy is around 50% at any time in the disease course[36, 37] and between 5% and 28% worldwide for receiving it in the last month of life, with 11% in the Netherlands.[38, 39] Systemic treatment at the end of life may result in increased hospital admissions and consequently, increased hospital deaths putting additional pressure on the healthcare system.[40-45] In many

countries, a substantial percentage of cancer patients die in the hospital[46, 47], for patients with lung cancer specifically it is found that between 28% and 87% died inside the hospital worldwide, with 28% in the Netherlands.[48]

Many studies have addresses indicators for 'aggressive care' at the end of life such as receiving systemic treatment in the last month of life, hospital admissions, emergency department visits and hospital deaths, which are related to poor quality of care.[49-52] For metastatic lung cancer patients with a poor prognosis, quality of death is an important factor and dying at home is considered as a quality indicator.[53] It is known that most patients would prefer to die at home.[44, 54-57] In 2012, the American Society for Clinical Oncology (ASCO) recommended to avoid the use of chemotherapy at the end of life to improve patient care.[58] In 2017 the ASCO guidelines recommend that '*patients with advanced cancer should receive dedicated palliative care service, early in the disease course, concurrent with active treatment'*.[59]

According to the World Health Organization (WHO), 'palliative care; is: '*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*'.[60] Several studies have shown that 'early palliative care', i.e. '*palliative support alongside standard cancer care shortly after a patient is diagnosed with incurable cancer*' may even improve overall survival.[61-63] A study of Temel et al. showed that among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood as compared with patients receiving standard care. Patients receiving early palliative care had less aggressive care at the end of life and even an improved overall survival. Both have their benefits and administering these therapies in conjunction could have the greatest benefit.

Treatment decisions and goals for treatment

Once the diagnosis is known, lung cancer patients receive information on the disease from their oncologist and a decision has to be made about treatment and care. The emotional impact of the diagnosis is huge for patients and therefore the information provided regarding the diagnosis, which may be complex, is often difficult for them to understand and remember.[64-69] For metastatic lung cancer patients, treatment should be aimed at life extension and/or improving quality of life without any prospect of curing the cancer. However, many patients receiving chemotherapy for incurable cancer do not understand that the treatment is unlikely to be curative.[70] Furthermore, there is contradictory research regarding the effects of chemotherapy treatment: in some studies systemic treatments appear to improve patient quality of life[71, 72], whereas other studies found no improvement or even a decline in quality of life.[6-9, 73] Research has shown that severely ill patients will often wish for treatment even if the treatment only has small benefits or is ineffective. Certain patients

are also willing to tolerate the toxicity for the hope of some life prolongation with quality of life as secondary importance.[74-76]

In summary, the decision whether to start or continue with a systemic treatment is complex and requires careful consideration of patient's expectations, preferences and values regarding the benefits and risks. Not much is known yet about the treatment incentives patients and oncologists have when starting a systematic treatment for an incurable disease and how well these thoughts are discussed. Since more treatment options have become available, treatment decisions in the last phase of life have become a delicate process. In the last few decades, patients satisfaction has become an important endpoint in the assessment of the quality of care.[77] It is of importance and yet not known to what extent certain treatment goals are achieved according to patients and oncologists after a systemic treatment and how satisfied they are on the choice that had been made to decide for a certain treatment.

The role of oncologists and relatives in treatment decisions for metastatic lung cancer

Proper communication by oncologists is crucial for the treatment decision process of patients with an incurable disease.[78] From literature it is known that oncologists may use complicated medical jargon when discussing prognosis and treatment options with a patient and sometimes even feel unprepared to have these discussions.[79,80] Oncologists may steer a patient towards choosing treatment and not properly explain alternatives because they want their patients to feel they are being helped and give them some hope, instead of them leaving with nothing, which can be perceived as withholding treatment.[81-83] Furthermore, patients with an incurable disease often have a poor prognostic perception as a result of deficiencies in doctor communication and attempts by patients and families to reduce the threat of death and maintain hope.[84] However, differences are found in the preferred level of communication participation between patient populations, for example based on age and educational level.[85] All these factors play a role in the patient's decision to start a systemic treatment for metastatic lung cancer and the goals and expectations patients have for that treatment. Furthermore, oncologists may start a treatment with different goals and expectations compared to their patient.[86] Direct questions from oncologists on the treatment goals may help patients more clearly define their goals and expectations for the treatment they wish to receive.[87]

As mentioned, cancer has a huge emotional impact on the patients but it also has a significant emotional impact on the relatives.[88, 89] Relatives often accompany patients to a clinical visit and help the patients obtain information relevant to medical treatments.[90-92] Once treatment has been started, patients' relatives often become the patients' caregiver and provide them with support and care.[93] Patients go through the different phases of the treatment together

with their relatives, thus a relative's evaluation of the treatment is also important and may differ from a patient's evaluation.

Objectives and research aims of this thesis

The overall aim of this thesis is to gain more insight into the use of systemic treatment for metastatic lung cancer patients in the context of the end of life. Research aims are to study:

1. The percentage of metastatic lung cancer patients who receive chemotherapy or TKIs in the last month of life in the Netherlands.
2. The percentage of metastatic lung cancer patients who die inside the hospital and whether hospital death is associated with receiving systemic treatment in the last month of life.
3. The type and feasibility of treatment goals that patients and their oncologists have when starting systemic treatment.
4. To what extent patients' and oncologists' treatment goals are achieved after systemic treatment and whether this differs between types of therapy. In addition, whether it was the right decision to start treatment in hindsight.
5. The perspective of the relatives in hindsight on the achievement of the patients' treatment goals and whether they are satisfied about the patients' treatment choice.

Methods

The data in this thesis is based upon two studies: a multicentre retrospective patient file study in ten hospitals in the Netherlands for the first two research aims (**chapter 2 and 3**) and a multicentre prospective longitudinal questionnaire and interview study on patients, oncologists and relatives in six hospitals in the Netherlands for the following three research aims (**chapter 4 – 6**).

The retrospective patient file study was performed in 2016 and 2017. Patients were included if they were diagnosed with metastatic lung cancer and died between the 1st of June 2013 and the 31st of July 2015. A total of 1322 patients were included in this study, ranging from 70 to 210 patients per hospital. Patient and healthcare characteristics such as age, gender, histology of the tumour, type of treatment, date of the last treatment and date of death were extracted from the patients' medical files.

The multicentre prospective longitudinal questionnaire and interview study was conducted between 2016 and 2019. Of the 374 eligible patients who started a systemic treatment for metastatic lung cancer, 266 patients and 23 of their prescribing oncologists participated (response of 71% and 100% respectively). Before starting a systemic treatment, both patients and oncologists received a questionnaire regarding what treatment goals they had and how

feasible they perceived these goals to be. After treatment, patients and oncologists were asked to what extent these treatment goals were achieved and if they were satisfied with the treatment decision made. Additionally, semi-structured interviews with 15 patients and 5 oncologists were performed to gain additional insight into the mentioned goals, the rate of achievement of these goals and the rationale on starting a treatment.

After the patient died a structured telephone interview was performed with a relative of the deceased patient. During the study period, 164 patients were deceased, resulting in 164 relatives being eligible for participation of which 118 participated in an interview (72% response). Relatives were asked to what extent they felt that the patients' treatment goals were achieved and if they were satisfied with the treatment choice made by the patient (figure 1).

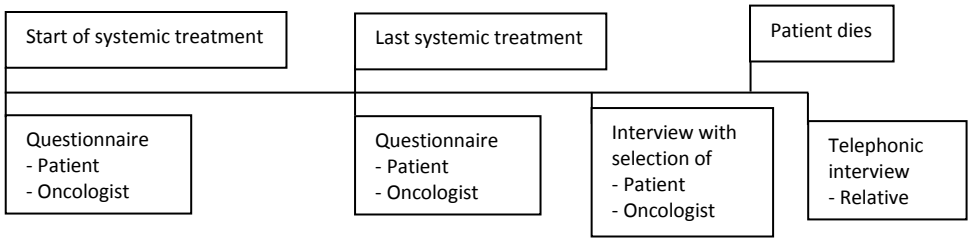

Figure 1. Graphic representation of the prospective study among patients, oncologists and relatives

Outline of this thesis

Chapter 2 presents the percentage of metastatic lung cancer patients who received chemotherapy or TKIs in the last month of life in the Netherlands. **Chapter 3** reports the percentage of metastatic lung cancer patients who died inside the hospital and whether hospital death is associated with receiving systemic treatment in the last month of life. **Chapter 4** focusses on the type and feasibility of treatment goals that patients and their oncologists have when starting a systemic treatment, the concordance between patients and oncologist concerning these goals and how feasible they think these goals are. **Chapter 5** describes to what extent patients' and oncologists' treatment goals are achieved and whether it was the right decision to start treatment in hindsight. **Chapter 6** elaborates on the perspective of the relatives in hindsight on the achievement of patients' treatment goals and whether they are satisfied with the patients' treatment choice. In the general discussion (**chapter 7**), the main findings from the preceding chapters are discussed. Additionally, methodological consideration and implications for practice and future research are formulated.

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CHEMOTHERAPY AND TYROSINE KINASE INHIBITORS IN THE LAST MONTH OF LIFE IN PATIENTS WITH METASTATIC LUNG CANCER: A PATIENT FILE STUDY IN THE NETHERLANDS

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Abstract

Objective: Chemotherapy in the last month of life for patients with metastatic lung cancer is often considered as aggressive end-of-life care. Targeted therapy with tyrosine kinase inhibitors (TKIs) is a relatively new treatment of which not much is known yet about use in the last month of life.

Aim: We examined what percentage of patients received chemotherapy or TKIs in the last month of life in the Netherlands.

Methods: Patient files were drawn from 10 hospitals across the Netherlands. Patients had to meet the following eligibility criteria: metastatic lung cancer; died between 1-6-2013 and 31-7-2015.

Results: From the included 1322 patients, 39% received no treatment for metastatic lung cancer, 52% received chemotherapy and 9% received TKIs. A total of 232 patients (18%) received treatment in the last month of life (11% chemotherapy, 7% TKIs). From the patients who received chemotherapy, 145 (21%) received this in the last month of life and 79 (11%) started this treatment in the last month of life. TKIs were given and started more often in the last month of life: from the patients who received TKIs, 87 (72%) received this treatment in the last month of life and 15 (12%) started this treatment in the last month of life.

Conclusion: A substantial percentage of patient received and even started chemotherapy or TKIs in the last month of life. For chemotherapy this might be seen as aggressive care. TKIs are said to have less side effects, do not lead to many hospital visits and due to the rapid response, are considered good palliation. However it is not known, yet possible that, when patients still receiving treatment until shortly before death, this might influence preparing for death in a negative way.

Introduction

Palliative chemotherapy, immunotherapy and targeted therapy with tyrosine kinase inhibitors (TKIs) are possible treatments for patients with metastatic cancer with the aim of relieving symptoms, temporary disease control and prolonging survival. However, it is difficult to balance the potential clinical benefit and potential harm due to side effects which may lead to a decreased quality of life (QOL).[1-4] Moreover, timed discontinuation of these treatments may be essential for patients to prepare for their death.[1] A recent study of Bekelman et al. (2016) showed that up to 12.7% of patients who died with cancer received chemotherapy in the last 30 days of life.[5] In 2012, the American Society for Clinical Oncology (ASCO) recommended to avoid the use of chemotherapy at the end-of-life to improve patients' care.[6] Mortality within one month after the last chemotherapy has been considered as an (negative) indicator of the quality of care.[7-9]

In case of lung cancer, whether chemotherapy near the end of life is appropriate is frequently discussed.[10] Metastatic lung cancer is an incurable disease associated with a high burden of symptoms, poor QOL and an estimated prognosis after the diagnosis of around 1 year.[11] According to national and international guidelines on lung cancer, patients with lung cancer can be treated with chemotherapy, immunotherapy (introduced in 2015) or TKIs. The availability of new anticancer agents (i.e. TKIs) has prolonged the timeline of medical treatment in metastatic cancer patients.[12-21] TKIs are oral drugs directed towards specific targetable protein driver mutations, such as EGFR and ALK mutations. Multiple clinical trials have shown that TKIs cause less side effects compared to chemotherapy and are less burdensome in time and traveling for the patient compared to in-hospital treatments. Above that, TKIs are associated with a 5-year survival of more than 50%.[16-21] Therefore, the urgency to discontinue these drugs in the last month of life may be less obvious compared to chemotherapy. Moreover, due to the expected fast response of TKIs, starting these drugs in patients with a targetable driver mutation might be beneficial to their quality of life, especially in patients with a poor performance score.

Studies of Bekelman et al. (2016) and Yang et al. (2013) reported respectively that within different countries 5.7% to 27.7% of patients who died with lung cancer were treated with palliative chemotherapy in the last month of life.[5, 10] Several studies attempt to identify the association between different patient characteristics and the use of palliative chemotherapy at the end of life. For instance, patients older than 75 years, women, unmarried patients, patients with a poor performance score and patients with comorbidities were less likely to receive palliative chemotherapy for metastatic lung cancer at the end of life.[1, 7, 22, 23] However, for TKIs less is known on how many patients who die of metastatic lung cancer were treated in the last month of life and which factors are associated with death within one month after the last treatment. A study among stage 3 and 4 lung cancer patients that started chemotherapy or TKIs as initial treatment showed that of patients who started chemotherapy 6.1% and of patients who started TKIs 8.6% died within 30 days after starting the initial

treatment.[24] Although 30 day mortality after initial treatment is not immediately comparable to the percentage of deceased patients who received treatment in the last month of life, this shows that treatment with TKIs in the last month of life also occurs.
In light of the above, we studied what percentage of patients with metastatic lung cancer receive chemotherapy or TKIs and what percentage of patients receive this in the last month of life. We also investigated which characteristics of patients, healthcare and oncologists are associated with receiving chemotherapy or TKIs in the last month of life.

Methods

Study design and population

We have conducted a retrospective patient file study in 10 hospitals across the Netherlands, 3 academic and 7 non-academic. We extracted demographic and clinical characteristics from medical files of patients who died of metastatic lung cancer. Medical files were selected based on Diagnosis Treatment Combinations (DBC) codes (DBC 1303 = Non-Small Cell Lung Cancer (NSCLC), DBC 1304 = Small Cell Lung Cancer (SCLC)) or International Classification of Diseases (ICD) codes, Ninth and Tenth Revision (ICD9 and ICD10 for (N)SCLC). Out of this selection, patients were included if they were diagnosed with metastatic lung cancer and died between the 1st of June 2013 and the 31st of July 2015. We excluded patients when they were not treated for lung cancer in the investigated hospital (n=123), when they were treated with an experimental drug for lung cancer (n=6), or when the date of the end of treatment was not known (n=18). A total of 1322 patients were included in this study, ranging from 70 till 210 patients per hospital.

Ethics, consent and permission

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, the Netherlands. According to the committee, obtaining informed consent of the family of the patients was not required since this study is based on medical files of patients who already died and data is handled anonymously.

Statistical methods

Statistical analyses were conducted using IBM SPSS statistics 22. Differences between the demographic characteristics of the study participants were tested with Analysis Of Variance (ANOVA) for the continuous variable age and with the chi-square test for dichotomous and nominal variables. A P-value of ≤0.05 denoted statistical significance. Generalized Estimated Equation (GEE) was used to attain understanding of the association between patient, healthcare and oncologist characteristics and the use of chemotherapy or TKIs in the last month of life. By using the 10 hospitals as a subject variable, GEE avoid the cluster effect present in the commonly used logistic regression models.

The dependent variable was the use of chemotherapy or TKIs in the last month of life. This variable was dichotomized in: 'use of medical treatment in the last month of life (yes/no)'. The independent variables were patient, healthcare and oncologist characteristics. Patient characteristics were sex (male/female), age (≤60, 61-70, ≥71), marital status (married/unmarried), comorbidity (yes/no), histology of the tumour (SCLC, NSCLC with targetable driver mutation (NSCLC+), NSCLC without targetable driver mutation (NSCLC-)) and performance status (ECOG (Eastern Cooperative Oncology Group) score 0, 1, 2, ≥3 or not known). When the performance status was described using the Karnofsky score, this was recoded into the ECOG score (90-100% = 0, 70-80%=1, 50-60% =2, 30-40%=3, 10-20%=4). Healthcare characteristics were type of medical treatment for metastatic lung cancer (none/chemotherapy/TKIs), started medical treatment in the last month of life (yes/no), line of medical treatment (first, second, third and more) and hospital type (academic/non-academic). Oncologist characteristics were sex (male/female) and age (≤40, 41-50, ≥51). Each statistically significant variable in the univariate GEE analyses ($p<0.10$) was entered into a multivariate GEE model. The final model was derived using the backward selection method, with a P-value of <0.05 as considered statistically significant. Results of the GEE analyses are presented as odds ratios (ORs) and associated 95% confidence intervals (CIs).

Results

Patient characteristics

From the 1322 patients with metastatic lung cancer 509 patients (39%) did not receive chemotherapy or TKIs for metastatic lung cancer. The remaining 813 patients received a systemic treatment: 692 patients received chemotherapy (52%) and 121 patients received TKIs (9%). The three groups (no treatment, chemotherapy and TKIs) show a statistically significant difference on all characteristics: patients receiving no treatment had a higher age at death (70 ± 10 years) compared to patients receiving chemotherapy or TKIs (65 ± 9 and 64 ± 10 years respectively). Moreover, a higher prevalence of comorbidity was observed in patients receiving no treatment (81%) compared to patients receiving chemotherapy or TKIs (72% and 61% respectively). From the patients who received TKIs, 41 patients (34%) did not have a targetable driver mutation (NSCLC-). Only 23 patients with a targetable driver mutation (NSCLC+) (5%) received no treatment. Chemotherapy was mostly administered to patients in the first line (65%) while TKIs were mostly administered in the third line (41%). Lastly, compared to patients receiving chemotherapy or TKIs (65% and 51% respectively), patients receiving no treatment were found more often in a non-academic hospital (78%) (table 1).

Table 1. Demographic characteristics of study participants (n=1322, column %)

Variable	No treatment†	Chemotherapy	TKIs	P
N	509 (39)	692 (52)	121 (9)	
Age – Years				
Mean ± SD	70±10	65±9	64±10	**<0.001**
Sex				
Male	313 (62)	422 (61)	56 (46)	
Female	196 (38)	270 (39)	65 (54)	**0.006**
Marital status‡				
Married	298 (71)	472 (78)	93 (85)	
Not married	123 (29)	136 (22)	17 (15)	**0.003**
ECOG performance score start				
0	23 (4)	118 (17)	22 (18)	
1	57 (12)	181 (26)	33 (27)	
2	47 (10)	75 (10)	18 (15)	
≥3	65 (13)	33 (5)	9 (8)	
Not known	300 (61)	285 (42)	39 (32)	**<0.001**
Comorbidity				
Yes	409 (81)	501 (72)	72 (61)	
No	99 (19)	191 (28)	47 (39)	**<0.001**
Tumour histology				
SCLC	42 (9)	222 (32)	0 (0)	
NSCLC+	23 (5)	79 (11)	80 (66)	
NSCLC-	412 (86)	390 (56)	41 (34)	**<0.001**
Line of treatment				
1st (490)		451 (65)	39 (33)	
2nd (185)		154 (22)	31 (26)	
≥ 3rd (134)	N.A.	85 (12)	49 (41)	**<0.001**
Hospital type				
Academic	113 (22)	242 (35)	59 (49)	
Non-academic	396 (78)	450 (65)	62 (51)	**<0.001**

TKIs: Tyrosine Kinase Inhibitors; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; NSCLC+: NSCLC with targetable driver mutation; NSCLC-: NSCLC without targetable driver mutation; N.A.: not applicable. †No treatment is defined as receiving no chemotherapy or TKIs for metastatic lung cancer. ‡ >5% missing values: marital status (14%). Bold values indicate a difference with a P-value of ≤0.05.

Percentage of patients receiving chemotherapy or TKIs in the last month of life

From all 1322 patients with metastatic lung cancer, 232 patients (18%) received chemotherapy or TKIs in the last month of life: 145 patients (11%) received chemotherapy and 87 patients (7%) received TKIs in the last month of life (figure 1a). From all the 692 patients who received chemotherapy at any time for metastatic lung cancer, 21% received this medical treatment in the last month of life (figure 1c). From all the 121 patients who received TKIs at any time for

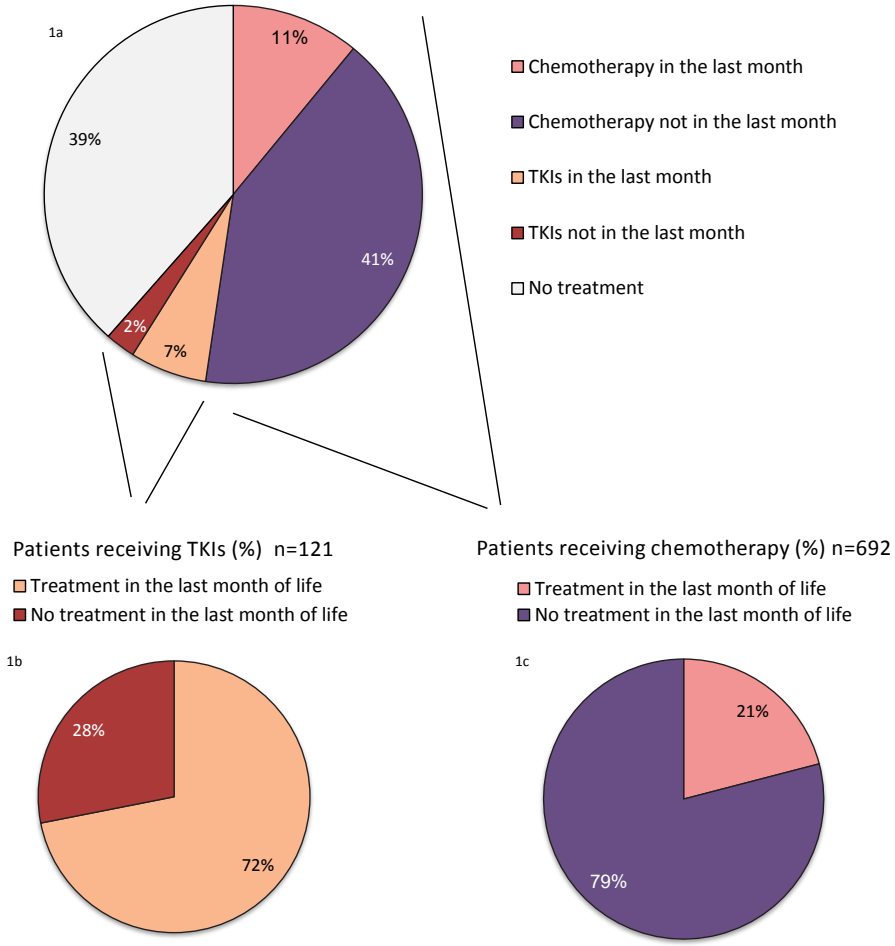

Figure 1. Percentages of patients receiving medical treatment

metastatic lung cancer, 72% received this medical treatment in the last month of life (figure 1b). From the 145 patients who received chemotherapy in the last month of life, 72 patients (50%) only received one cycle (data not shown).

We also looked at the time between initiation of the treatment and death: from the 692 patients who received chemotherapy at any time for metastatic lung cancer, 79 patients (11%) died within one month after start of the chemotherapy. From the 121 patients who received TKIs at any time for metastatic lung cancer, 15 patients (12%) died within one month after start of TKIs. Of these 15 patients, 8 patients had NSCLC+ and 7 patients had NSCLC-. When treatment was given in the last month of life, this treatment was started in the last month of life in 54% in case of chemotherapy (n=79) and in 17% in case of TKIs (n=15).

Association between the characteristics of the population and receiving chemotherapy or TKIs in the last month of life

In the multivariate model, most variables were not associated with receiving chemotherapy or TKIs in the last month of life, except for histology of the tumour and type of treatment: patients with NSCLC- had a 0.439 lower odds (p=0.003) of receiving chemotherapy or TKIs in the last month of life compared to patients with SCLC. Patients receiving TKIs had a 9.503 higher odds (p<0.001) of receiving this treatment in the last month of life, compared to patients receiving chemotherapy (table 2). Therefore we decided to do a separate GEE analysis for patients receiving chemotherapy and TKIs. From these patients receiving TKIs in the last month of life, 25 patients (29%) had NSCLC- (data not shown).

Association between the characteristics of the population and receiving chemotherapy in the last month of life

Histology of the tumour and line of treatment were associated with receiving chemotherapy in the last month of life. Patients with NSCLC- had a 0.468 lower odds (p=0.009) of receiving chemotherapy in the last month of life compared to patients with SCLC. Patients who received third-line chemotherapy had a 2.016 higher odds (p=0.013) of receiving chemotherapy in the last month of life compared to patients receiving first-line chemotherapy (table 3).

Association between the characteristics of the population and receiving TKIs in the last month of life

Tumour histology, line of treatment and age of the oncologist were associated with receiving TKIs in the last month of life. Patients with NSCLC+ had a 2.529 higher odds (p=0.001) of receiving TKIs in the last month of life compared to patients with NSCLC-. Patients who received TKIs in the last month of life had a 1.723 higher odds (p=0.042) of receiving this in the second line than in the first line. From the patients who received TKIs in the second line, 15 patients (48%) had NSCLC-. From the patients who received TKIs in the third line, 19 patients (39%) had NSCLC-. Patients with a prescribing oncologist in the age range of ≤40 and 41-50 had respectively a 3.238 and 2.841 higher odds (p=0.036; p=0.027) of receiving TKIs in the last month of life compared to patients with a prescribing oncologist in the age range of ≥ 51 (table 4).

Table 2. Univariate and multivariate GEE analyses of factors associated with receiving **chemotherapy or TKIs** in the last month of life

N=813 Variable (N)	Patients receiving medical treatment in the last month of life (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Sex			
Female (335)	31	1.068 (0.923 – 1.236)	
Male (478)	27	1.0	
Age–years			
≤60 (231)	32	1.308 (0.949 – 1.801)	
60-71 (318)	29	1.147 (0.827 – 1.590)	
≥71 (264)	25	1.0	
Marital status			
Not married (153)	26	1.0	
Married (565)	30	1.162 (0.740 – 1.825)	
Comorbidity			
No (238)	20	1.014 (0.657 – 1.566)	
Yes (573)	16	1.0	
Tumour histology			
SCLC (222)	29	1.0	1.0
NSCLC+ (159)	51	**2.212 (1.163 – 4.210)***	0.817 (0.284 – 2.350)
NSCLC- (431)	20	**0.593 (0.390 – 0.92)***	**0.439 (0.257 – 0.751)****
Line of treatment			
1st (490)	22	1.0	
2nd (185)	31	**1.560 (1.219 – 1.997)***	
≥ 3rd (134)	46	**2.510 (1.528 – 4.123)***	
Sex oncologist			
Female (196)	26	1.0	
Male (575)	29	1.105 (0.668 – 1.829)	
Age category oncologist			
≤ 40 (106)	33	1.129 (0.701 – 1.819)	
41–50 (296)	26	0.945 (0.579 – 1.541)	
≥ 51 (369)	29	1.0	
Hospital type			
Academic (301)	35	1.435 (0.622 – 3.308)	
Non-academic (512)	25	1.0	
Type of treatment			
Chemotherapy (692)	21	1.0	1.0
TKIs (121)	72	**8.182 (5.694 – 11.756)***	**9.503 (5.156 – 17.517)****

OR: odds ratio; CI: confidence interval; TKIs: Tyrosine Kinase Inhibitors; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; NSCLC+: NSCLC with targetable driver mutation; NSCLC-: NSCLC without targetable driver mutation. * P-value of ≤0.10; ** P-value of ≤0.05

Table 3. Univariate and multivariate GEE analyses of factors associated with receiving **chemotherapy** in the last month of life

N=692 Variable (N)	Patients receiving medical treatment in the last month of life (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Sex			
Female (270)	22	1.085 (0.814 – 1.445)	
Male (422)	20	1.0	
Age–years			
≤60 (188)	22	1.204 (0.756 – 1.918)	
61-70 (270)	22	1.198 (0.824 – 1.741)	
≥71 (234)	19	1.0	
Marital status			
Not married (136)	21	1.018 (0.660 – 1.572)	
Married (472)	22	1.0	
Comorbidity			
No (191)	19	1.0	
Yes (501)	22	1.208 (0.702 – 2.080)	
Tumour histology			
SCLC (222)	29	1.0	1.0
NSCLC+ (79)	24	0.563 (0.238 – 1.329)	0.664 (0.216 – 2.043)
NSCLC- (390)	16	**0.442 (0.277 – 0704)***	**0.468 (0.265 – 0.828)****
Line of treatment			
1st (451)	18	1.0	1.0
2nd (154)	21	1.243 (0.831 – 1.861)	1.050 (0.646 – 1.709)
≥ 3rd (85)	34	**2.072 (1.287 – 3.336)***	**2.016 (1.157 – 3.513)****
Sex oncologist			
Female (178)	20	1.0	
Male (484)	21	1.095 (0.764 – 1.571)	
Age category oncologist			
≤ 40 (91)	24	1.205 (0.775 – 1.873)	
41 – 50 (263)	19	0.885 (0.576 – 1.360)	
≥ 51 (307)	22	1.0	
Hospital type			
Academic (242)	25	1.357 (0.605 – 3.042)	
Non-academic (450)	19	1.0	

OR: odds ratio; CI: confidence interval; TKIs: Tyrosine Kinase Inhibitors; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; NSCLC+: NSCLC with targetable driver mutation; NSCLC-: NSCLC without targetable driver mutation. * P-value of ≤0.10; ** P-value of ≤0.05

Table 4. Univariate and multivariate GEE analyses of factors associated with receiving **TKIs** in the last month of life

N=121 Variable (N)	Patients receiving medical treatment in the last month of life (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Sex			
Female (65)	65	**0.436 (0.201 – 0.945)***	
Male (56)	80	1.0	
Age–years			
≤60 (43)	74	1.033 (0.317 – 3.361)	
61-70 (48)	69	0.773 (0.282 – 2.116)	
≥71 (30)	73	1.0	
Marital status			
Not married (17)	65	1.0	
Married (93)	73	1.496 (0.426 – 5.253)	
Tumour histology			
NSCLC + (80)	79	**2.211 (1.242 – 3.934)***	**2.529 (1.448 – 4.639)****
NSCLC - (41)	61	1.0	
Comorbidity			
No (47)	70	1.0	
Yes (72)	72	1.102 (0.586 – 2.071)	
Line of treatment			
1st (39)	72	1.0	1.0
2nd (31)	81	**1.670 (1.025 – 2.719)***	**1.723 (1.019 – 2.912)****
≥ 3rd (49)	67	0.836 (0.343 – 2.047)	1.188 (0.520 – 2.712)
Sex oncologist			
Female (18)	83	1.775 (0.846 – 3.723)	
Male (91)	73	1.0	
Age category oncologist			
≤ 40 (15)	87	**3.553 (1.106 – 11.414)***	**3.238 (1.081 – 9.698)****
41 – 50 (33)	85	**2.848 (1.068 – 7.599)***	**2.841 (1.123 – 7.184)****
≥ 51 (62)	66	1.0	1.0
Hospital type			
Academic (59)	75	1.374 (0.712 – 2.641)	
Non-academic (62)	70	1.0	

OR: odds ratio; CI: confidence interval; TKIs: Tyrosine Kinase Inhibitors; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; NSCLC+: NSCLC with targetable driver mutation; NSCLC-: NSCLC without targetable driver mutation. * P-value of ≤0.10; ** P-value of ≤0.05

Discussion

From the 1322 patients included in this study, 39% received no treatment for metastatic lung cancer, 52% received chemotherapy and 9% received TKIs. In total, 18% received treatment in the last month of life (11% chemotherapy and 7% TKIs). When treatment was given, TKIs were (still) given more often in the last month of life than chemotherapy (72% versus 21%). When treatment was (still) given in the last month of life, this treatment was started in the last month of life in 54% in case of chemotherapy and in 17% in case of TKIs.

Our study found a percentage of patients receiving chemotherapy in the last month of life that falls within the range of rates found for patients with lung cancer in other studies (between 5.7% and 27.7%).[5, 10] The rate of 11% that we found for the Netherlands is somewhat lower than the one of 16,4% found by Bekelman et al. (2016).[5] This might be due to the difference in methods; making use of administrative claims data as they did in that study gives less precise information on the exact date a treatment is started or stopped than a patient file study. The percentages found in both studies show that the Netherlands are not among the countries with the lowest percentages such as Canada (5.9%) or Norway (5.7%).[5]

To our knowledge there are no studies with which we can compare our finding of 7% of patients who died with metastatic lung cancer that had TKIs in the last month of life. This percentage seems low, but this is for a large part due to TKIs not being given so often to this patient group (9% TKIs and 52% chemotherapy).

We found that patients who received TKIs had an odds ratio of 9.5 to still receive therapy in the last month of life compared to patients receiving chemotherapy. A salient finding is that from patients receiving TKIs in their last month, 71% did not have a targetable driver mutation. However, these patients did not receive their TKIs in the first line. Knowing the rate of success is low in this group, it is debatable whether this should be considered good practice.[25] This result resonates with findings of Choi et al. that the time between stopping TKIs and death is shorter compared to the time between stopping chemotherapy and death: being 19 days compared to 35 days respectively.[22] Burgers et al. also found a higher odds (OR=1.3) of TKIs compared to chemotherapy with regard to 30 day mortality after the start of the initial treatment.[24]

TKIs are believed to extend survival with less toxicity and a higher quality of life in patients with a specific targetable protein driver mutation. If effective, they usually show a rapid response which makes it suitable for patients with a poor performance score. Therefore, oncologists may be reluctant to stop this medication even when it is close to the end of life. Another reason of reluctance to stop might be that a disease flare after TKIs discontinuation may occur.[26] Although nausea, vomiting, myelosuppression and alopecia generally occur

less frequently than with chemotherapy, TKIs are associated with side effects such as skin problems, chronic diarrhoea, fatigue and electrolyte imbalances that should not be ignored.[27] The risk of side effects may also increase closer to the end of life due to altered metabolism and interaction with other prescribed medication.[28] On the other hand, in a study of Shaw et al. (2013), patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with Crizotinib (a TKI) than with chemotherapy.[21] However, even with a five-year survival of >50%, timely discontinuation of these treatments may be essential to patients for a dignified leave of their loved ones and life itself.[1] Therefore, more research is needed about the consequences of continuation of TKIs shortly before death. Only then it is possible to consider whether not giving TKIs shortly before death should be a quality indicator for appropriate end-of-life care, as is not giving chemotherapy shortly before death.[29] Our result, that in 54% of patients who received chemotherapy in the last month of their life this treatment also had started in the last month of life, is an indication of overtreatment and supports the relevance of this quality indicator and the recommendations of ASCO.[6]

Patients who received third-line chemotherapy, had higher odds (OR=2.084) of receiving chemotherapy in the last month of life compared to patients receiving first-line chemotherapy. In this case it might play a role that patients with already a poor performance status were given chemotherapy as a final option for maintaining hope and therefore died shortly after the last chemotherapy cycle. SCLC patients may have received chemotherapy for attempted symptom control, which might explain the lower odds of NSCLC patients receiving chemotherapy. Patients with a prescribing oncologist aged ≤50 had a higher odds of receiving TKIs in the last month of life compared to patients with a prescribing oncologist aged ≥51. A possible explanation might be that younger oncologists are better up to date compared to their older colleagues when it comes to TKIs.

The high number of patients analysed in this study (1322) among ten different hospital sites makes the results robust and generalizable. Since all patients diagnosed with metastatic lung cancer were included in this study, there is no selection bias. However, this study has some potential limitations. First, the inevitable limitation of a patient file study is that we are not able to discover the rationale of the patient and the oncologist behind starting and stopping of chemotherapy or TKIs. Secondly, data on performance status could not always be retrieved from medical records due to the absence of documentation. Thirdly, we only documented the last treatment line, therefore we do not know what treatments patients received in earlier treatment lines.

In conclusion, our study gives indications of overtreatment at the end of life. An indicator is that more than half of patients who received chemotherapy in the last month of life also started this treatment in the last month of life. Also that the choice of the treatment among

others depends on non-patient related factors such as age of the oncologist might be an indication of overtreatment. Additionally, a high percentage of patients treated with TKIs did not fulfil appropriate criteria for starting this type of treatment, which might indicate overtreatment of negative driver mutation patients. Especially when chemotherapy is started shortly before death this can be seen as aggressive care. TKIs are said to have less side effects and do not lead to many hospital visits. Therefore, it is debatable whether TKIs started shortly before death should be considered as aggressive treatment. However, when still receiving it until shortly before death, this might influence preparing for death in a negative way. It is important to study whether this is the case. Although this study describes the Dutch situation, the percentages of receiving a medical treatment for metastatic lung cancer are informative for other countries.

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3

IS IN-HOSPITAL MORTALITY HIGHER IN PATIENTS WITH METASTATIC LUNG CANCER WHO RECEIVED TREATMENT IN THE LAST MONTH OF LIFE? A RETROSPECTIVE COHORT STUDY

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Abstract

Objective: Metastatic lung cancer is an incurable disease which results in a high burden of symptoms, a poor quality of life and an expected prognosis of less than 1 year after diagnosis. Treatment shortly before death may result in potential burdensome and inappropriate hospital admissions and hospital deaths. Dying at home is, at a population level, considered a quality for good end-of-life care.

Aim: We examined what percentage of patients with metastatic lung cancer died inside the hospital and if hospital death, or other characteristics of the patient, oncologist or healthcare, were associated with treatment in the last month of life.

Methods: This retrospective cohort study evaluated the medical records of 1322 patients with metastatic lung cancer who received care at one of 10 hospitals across the Netherlands and died between 1-6-2013 and 31-7-2015. Demographic and clinical characteristics were obtained from the medical records.

Results: In total, 18% of the patients died during a hospital admission. This percentage was higher for patients who received chemotherapy (42%) or targeted therapy with Tyrosine Kinase Inhibitors (25%) in the last month of life. Patients younger than 60 years of age, patients who received chemotherapy in the last month of life and patients in whom TKIs were started in the last month of life were more likely to die inside the hospital.

Conclusion: In the Netherlands, fewer than one in five patients with metastatic lung cancer died in the hospital and in-hospital death was associated with the relatively late use of chemotherapy or targeted therapy. Careful selection of patients for disease-modifying therapy might enhance the opportunity for patients to die at their preferred place.

Introduction

Metastatic lung cancer is an incurable disease and the leading cause of death from cancer worldwide. This disease results in a high burden of symptoms, a poor quality of life and an expected prognosis of less than 1 year after diagnosis.[1,2] Treatment is focused on relieving symptoms, temporary disease control, and prolonging lifespan. According to international guidelines on lung cancer palliative chemotherapy, immunotherapy (introduced in 2015) and/or targeted therapy with Tyrosine Kinase Inhibitors (TKIs) directed towards specific targetable protein driver mutations (such as EGFR and ALK mutations) are treatments of choice.[3-6] Aggressive treatment shortly before death is increasing over time[7] and may result in potential burdensome and inappropriate hospital admissions and consequently hospital deaths, which could be a threat to good end-of-life care.[8-10]

In many countries a substantial part of patients with cancer die in hospitals,[11,12] whereas most patients prefer to die at home.[13-17] In a study of Cohen et al. (2017) between 27.5% (New Zealand) and 86.5% (Korea) of patients with lung cancer died inside a hospital, with 28% of patients in the Netherlands.[18] For metastatic lung cancer patients with a poor prognosis, quality of death is an important factor and dying at home is considered, at population level, as a quality indicator.[19] Multiple studies present factors influencing the probability of death at home, with anti-cancer treatment in the last phase of life as one of the factors that may hinder patients to die at home.[20-22] Results from a systematic review about determinants of home and nursing-home death indicate that there are no studies available on factors associated with hospital deaths specifically for patients with metastatic lung cancer.[23,24]

Therefore, we conducted a multicentre study in the Netherlands to examine what percentage of patients with metastatic lung cancer died inside the hospital, what percentage received a treatment for metastatic lung cancer and what percentage received chemotherapy or TKIs in the last month of life. We also examined if hospital death is associated with receiving treatment in the last month of life and other patients, healthcare and oncologists characteristics.

Methods

Study design and population

We conducted a patient medical file study in 10 hospitals across the Netherlands, 3 academic and 7 non-academic hospitals. We gathered demographic and clinical characteristics from medical files of patients who died of metastatic lung cancer. Medical files were selected based on Diagnosis Treatment Combinations (DBC) codes (DBC 1303 = Non-Small Cell Lung Cancer (NSCLC), DBC 1304 = Small Cell Lung Cancer (SCLC)) or International Classification of Diseases (ICD) codes, Ninth and Tenth Revision (ICD9 and ICD10 for (N)SCLC). Out of this selection, patients were included if they were diagnosed with metastatic lung cancer and died between

the 1st of June 2013 and the 31st of July 2015. A two-year time frame was chosen to assure a sufficient sample size. We excluded patients who were referred to another hospital for a second opinion and therefore might receive a medical treatment elsewhere (n=123), who were treated with an experimental drug for lung cancer (n=6), or if the date of the end of treatment was not known (n=18). A total of 1322 patients were included in this study, ranging from 70 to 200 patients per hospital.

Ethics, consent and permission

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, the Netherlands. According to the committee, obtaining informed consent of the family of the patients was not required since this study is based on medical files of patients who already died and data is handled anonymously.

Statistical methods

Statistical analyses were conducted using IBM SPSS statistics 22. Frequencies were used for the descriptive statistics in table 1. Generalized Estimated Equation (GEE) was used to attain understanding of the association between patient, healthcare and oncologist characteristics and the place of death. By using the 10 hospitals as a subject variable, GEE accounts for the cluster effect present in the commonly used logistic regression models.

The dependent variable was the place of death. This variable was dichotomized in: 'died in hospital (yes/no)'. The independent variables were patient, healthcare and oncologist characteristics. Patient characteristics were sex (male/female), age (≤60, 61-70, ≥71), marital status (married/unmarried), comorbidity (yes/no) and histology of the tumour (SCLC, NSCLC with targetable driver mutation (NSCLC+), NSCLC without targetable driver mutation (NSCLC-)). Healthcare characteristics were type of medical treatment for metastatic lung cancer (none/chemotherapy/TKIs), received medical treatment in the last month of life (no/yes; chemotherapy/yes; TKIs), started medical treatment in the last month of life (no/yes; chemotherapy/yes; TKIs), line of medical treatment (first, second, third and more), and hospital type (academic/non-academic). Oncologist characteristics were sex (male/female) and age (≤40, 41-50, ≥51). Hospital type and oncologists characteristics were included in the analyses since policies and treatment preferences may very between academic-, non-academic hospitals and oncologists characteristics respectively.

Each statistically significant variable in the univariate GEE analyses ($p<0.10$) was entered into a multivariate GEE model. The final model was derived using the backward selection method, with a P-value of <0.05 as considered statistically significant. Results of the GEE analyses are presented as odds ratios (ORs) and associated 95% confidence intervals (CIs).

Results

Patient characteristics

From the 1322 patients with metastatic lung cancer, 692 patients (52%) received chemotherapy, 121 patients (9%) received TKIs and 509 patients (39%) received neither. From the patients who did receive chemotherapy or TKIs, 232 patients (18%) received this in the last month of life. A total of 79 patients (6%) and 15 patients (1%) started chemotherapy or TKIs in the last month of life (table 1).

Table 1. Demographic characteristics of study participants (n=1322)

Variable	N (%)
Sex	
Male	791 (60)
Female	531 (40)
Age–Years	
≤60	307 (23)
61-70	487 (37)
≥71	528 (40)
Marital status*	
Married	863 (76)
Not married	276 (24)
Comorbidity	
Yes	982 (74)
No	337 (26)
Tumour histology	
SCLC	264 (21)
NSCLC with targetable mutation	182 (14)
NSCLC without targetable mutation	843 (65)
Treatment for metastatic lung cancer	
Chemotherapy	692 (52)
TKI	121 (9)
None**	509 (39)
Treatment received in the last month	
Yes; chemotherapy	145 (11)
Yes; TKIs	87 (7)
No	1090 (82)
Treatment started in the last month	
Yes; chemotherapy	79 (6)
Yes; TKIs	15 (1)
No	1228 (93)
Line of treatment	
1st	490 (37)
2nd	185 (14)
≥ 3rd	134 (10)
Hospital type	
Academic	414 (31)
Non-academic	908 (69)

SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors.
*: >5% missing values: marital status (14%); **None is defined as receiving no medical treatment for metastatic lung cancer

Percentage of patients who died inside the hospital or at any other place

From all 1322 patients with metastatic lung cancer 239 patients (18%) died inside the hospital (figure 1a). No difference was found stratified for patients receiving any treatment or no treatment (figure 1b). Patients receiving TKIs showed a larger percentage (21%) of hospital deaths compared to patients receiving chemotherapy (18%) (not shown). However, a difference was seen when patients received any treatment in the last month of life; 36% of these patients died inside the hospital (figure 1c). From the 145 patients who received chemotherapy in the last month of life, 61 patients (42%) died in the hospital (figure 1d). From the 87 patients who received TKIs in the last month of life, 22 patients (25%) died inside the hospital (figure 1d).

Association between the characteristics of the population and hospital death

Age, treatment in the last month of life and treatment started in the last month of life were associated with death inside the hospital. Patients ≤60 years had a 1.233 times higher odds ($p=0.039$) for death inside the hospital compared to patients with an age of ≥71 years. Patients who received chemotherapy in the last month of life had a 3.355 times higher odds ($p<0.001$) for death inside the hospital compared to patients who did not received a treatment in the last month of life. Patients in whom TKIs were started in the last month of life had a 9.911 times higher odds ($p<0.001$) for death inside the hospital compared to patients who did not started a treatment in the last month of life (table 2). From these patients in whom TKIs were started in the last month of life and died inside the hospital, 1 patient received this treatment in the first line, 5 patients in the second line and 4 patients in the third line or more.

Discussion

Our study showed that 18% of patients with metastatic lung cancer died inside the hospital which was independent of receiving treatment or not. Furthermore, 42% of patients who received chemotherapy and 25% of patients who received TKIs in the last month of life died inside the hospital. Patients younger than 60 years of age, patients who received chemotherapy in the last month of life and patients in whom TKIs were started in the last month of life had a higher odds to die inside the hospital.

In 2008, 28% of lung cancer patients died inside the hospital in the Netherlands.[18] This is a higher percentage compared to the results of our study where we show that in 2013-2015 18% of patients with metastatic lung cancer died inside the hospital. This decrease in hospital deaths in 5 to 8 years' time may be explained by the increased awareness of palliative care in general and the developments in home care.

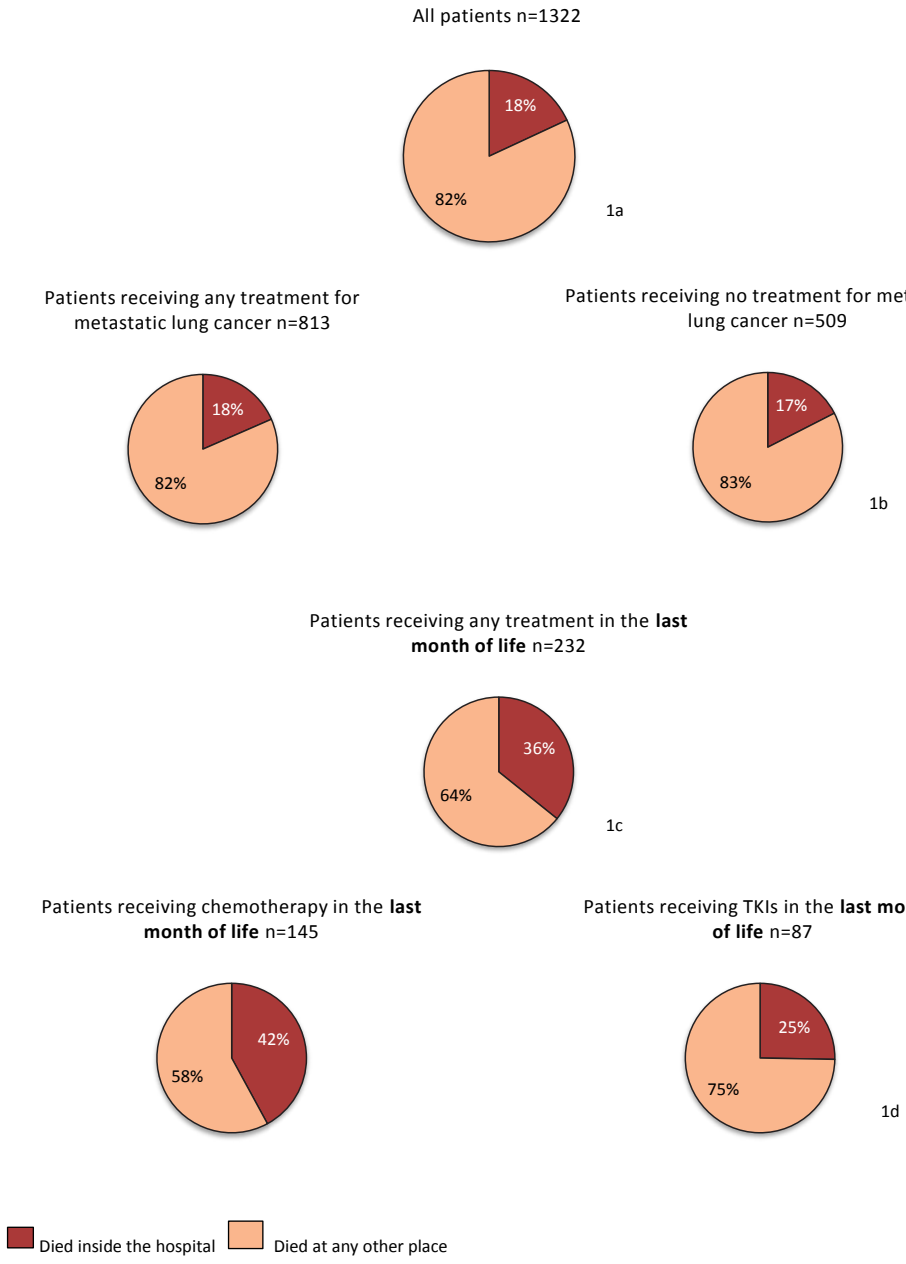

Figure 1. Percentages of patients with metastatic lung cancer who died inside the hospital or at any other place

Table 2. Univariate and multivariate GEE analyses of factors associated with hospital death

N=1322 Variable (N)	Patients who died in the hospital (row %)	Univariate OR (95%-CI)	p-value	Multivariate OR (95%-CI)	p-value
Sex					
Female (531)	17	1.0			
Male (791)	19	1.161 (0.927 – 1.454)	0.193		
Age–years					
≤60 (307)	20	1.346 (1.140 – 1.590)	**<0.001**	1.233 (1.011 – 1.503)	**0.039**
61-70 (487)	20	1.348 (1.048 – 1.732)	**0.020**	1.229 (0.978 – 1.544)	0.077
≥71 (528)	15	1.0		1.0	
Marital status					
Married (863)	18	1.0			
Not married (276)	20	1.105 (0.697 – 1.754)	0.671		
Comorbidity					
No (337)	19	1.0			
Yes (982)	17	1.139 (0.878 – 1.477)	0.328		
Tumour histology					
SCLC (264)	21	1.0			
NSCLC with targetable mutation (182)	16	0.574 (0.302 – 1.092)	**0.091**		
NSCLC without targetable mutation (843)	18	0.791 (0.575 – 1.089)	0.150		
Treatment received for metastatic lung cancer					
None (509)	18	1.0			
Chemotherapy (692)	18	1.064 (0.788 – 1.438)	0.686		
TKI (121)	22	1.221 (0.761 – 1.959)	0.408		
Treatment in the last month of life					
No (1090)	14	1.0		1.0	
Yes; chemotherapy (145)	42	4.406 (2.796 – 6.944)	**<0.001**	3.355 (2.332 – 4.827)	**<0.001**
Yes; TKI (87)	25	2.038 (0.975 – 4.258)	**0.058**	1.159 (0.634 – 2.090)	0.623
Treatment started in the last month of life					
No (1228)	16	1.0		1.0	
Yes; chemotherapy (79)	47	4.626 (2.471 – 8.662)	**<0.001**	1.534 (0.936 – 2.515)	0.089
Yes; TKI (15)	67	11.878 (4.012 – 35.169)	**<0.001**	9.911 (3.960 – 24.801)	**<0.001**

Continue

Continued

N=1322 Variable (N)	Patients who died in the hospital (row %)	Univariate OR (95%-CI)	p-value	Multivariate OR (95%-CI)	p-value
Line of treatment					
1st (490)	19	1.0			
2nd (185)	20	1.091 (0.540 – 2.206)	0.808		
≥ 3rd (134)	16	0.807 (0.504 – 1.293)	0.373		
Hospital type					
Non-academic (908)	16	1.0			
Academic (414)	22	1.429 (0.900 – 2.270)	0.130		
Sex oncologist					
Female (327)	16	1.0			
Male (919)	18	1.215 (0.714 – 2.065)	0.473		
Age category oncologist					
≤ 40 (181)	20	1.158 (0.717 – 1.870)	0.548		
41 – 50 (479)	17	1.082 (0.655 – 1.788)	0.757		
≥ 51 (585)	17	1.0			

OR: odds ratio; CI: confidence interval; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.10 for the univariate model and with a p-value of ≤0.05 for the multivariate model.

In total, 18% of patients received a medical treatment for metastatic lung cancer within the last month of life and 7% started this treatment in the last month of life. This is comparable to the work of Earle et al.[7]

Our finding that patients receiving chemotherapy in the last month of life have higher odds for hospital death confirms findings from earlier studies that receiving chemotherapy in the last month of life is associated with a reduced likelihood of home death.[6,19,25] In interpreting this result it is important to realize that the fact that a high percentage of home deaths is considered a quality indicator of care at the end of life and does not mean that all hospital deaths should be avoided. On an individual level it is possible that dying in a hospital is an informed decision. Although most patients prefer to die at home,[16] hospital death may not always equal poor quality of death. A recent study showed that family members were satisfied with the quality of care patients received when they died inside the hospital. Symptoms were well managed overall and their loved ones were treated with kindness and respect.[26] There are several possible explanations for the relation between treatment in the last month of life and hospital death. Potentially the aggressive character of the treatment increases the risk of hospitalization for the treatment of side effects.[5] Another explanation may be that when a patient is treated for lung cancer, the oncologist is still the main care provider and the patient has to come to the hospital now and then, making it more natural to go and stay in the hospital when problems occur. Patients in whom treatment for lung cancer is not started or stopped are referred back to the general practitioner. In an evaluation study from England, general practitioners mentioned that when one of their patients was hospitalized, they were rarely contacted by the hospital physicians about the patients' medical situation. Palliative care in the home setting becomes more difficult to accomplish in this scenario.[27]

Previous studies showed that patients with metastatic cancer who were receiving palliative chemotherapy and died inside the hospital are more likely to be younger compared to patients who did not received chemotherapy.[6,28,29] One possible explanation may be that oncologists and/or patients do not want 'to give up' when patients are relatively younger resulting in starting and/or continuing treatment in the last month of life leading to a higher chance of hospital deaths.

To our knowledge, studies showing higher odds ratios of hospital deaths in patients in whom TKIs were started in the last month of life have not yet been published. Our dataset does contain patients in whom TKIs are started in the last month of life and died inside the hospital. However, this is only a small number (n=15). The use of TKIs might have increased over the past years due to rapid developments in this field while our data stems from 2013-2015. To draw firm conclusions from this outcome, more research is needed.

The high number of patients analysed in this study (n=1322) among ten different hospital sites makes the generalizability of the results large. By including 3 academic hospitals and 7 non-academic hospital distributed across the North, East, South and West of the Netherlands, we assume that it is a representative sample of the Dutch population with metastatic lung cancer. Since all patients diagnosed with metastatic lung cancer were included in this study, selection bias is minimised. To our knowledge, this is the first study that shows factors associated with hospital death in patients with metastatic lung cancer. At the same time, this study has some limitations. First, because of the retrospective study design we are not informed on the preferred place of death. Second, we had information on several possible covariates or confounders, but it would have been good to have information on more. This is related to the limitations of a patient medical file study. For instance, data on performance status could not always be retrieved from medical records due to absence of documentation. Patients with a poor performance status might have a higher risk to be hospitalized with death inside the hospital as a consequence. Other potentially relevant covariates or confounders are among others symptom burden, date of diagnosis, ethnicity and socioeconomic circumstances.

In conclusion, our study shows that a substantial percentage of patients who received chemotherapy or TKIs in the last month of life died inside the hospital. Patients in whom TKIs were started in the last month of life even had a higher odds ratio of dying inside the hospital compared to patients who did not start in the last month of life. While these treatments can be started with a palliative intent, a reluctant attitude towards treatment for metastatic lung cancer at the end of life might enhance the opportunity for patients to die at home, the preferred place of most people.[13-17] Although this study describes the Dutch situation, the percentages of hospital deaths for patients with metastatic lung cancer are informative for other countries.

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4

WHAT GOALS DO PATIENTS AND ONCOLOGISTS HAVE WHEN STARTING MEDICAL TREATMENT FOR METASTATIC LUNG CANCER?

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Abstract

Objective: Metastatic lung cancer is an incurable disease and can be treated with systemic therapy. These treatments might prolong survival and reduce symptoms, but may also cause serious side effects.

Aim: We studied the treatment goals of metastasized lung cancer patients and their oncologists before starting systemic therapy, concordance between patients' and oncologists' goals and feasibility of these goals.

Methods: This research was conducted between November 2016 and April 2018 in one academic and five non-academic hospitals across the Netherlands. A total of 266 patients with metastatic lung cancer and their prescribing oncologists (n=23) filled out a questionnaire about their treatment goals and the estimated feasibility of these goals before treatment was started. Additional interviews were conducted with patients and oncologists.

Results: Patients and oncologists reported 'quality of life' (45%;72%), 'life prolongation'(45%; 55%), 'decrease in tumour size' (39%; 66%) and 'cure' (19%; 2%) as treatment goals. The interviews showed that the latter appeared to be often as motivation to stay alive. Concordances between patients' and oncologists' treatment goals were low (ranging from 24% to 33%). Patients had slightly higher feasibility scores than oncologists (6.8 vs 5.8 on a 10-point scale). Educational level, age, religious views and performance status of patients were associated with treatment goals.

Conclusion: Patients and oncologists set various goals for the treatment they receive/ prescribe. Low concordance might exist because different goals are set or due to misunderstanding by the patient. Clear communication about treatment goals should be integrated into clinical care.

Introduction

In the Netherlands, over 13,000 patients are diagnosed with lung cancer every year.[1] Early symptoms of lung cancer are non-specific and therefore diagnosis is often made when the disease is already in an advanced stage.[2] Metastatic lung cancer (stage IV lung cancer) is an incurable disease and the leading cause of cancer related death worldwide. It often results in a high burden of symptoms, a poor quality of life and an expected prognosis of less than 1 year after diagnosis.[3 4]

Chemotherapy, targeted therapy with Tyrosine Kinase Inhibitors (TKIs), and immunotherapy are possible treatments for patients with metastatic lung cancer with the aim of relieving symptoms, temporary disease control, maintaining or improving quality of life (QOL) and prolonging survival. [5-9] These treatments have various side effects and different overall survival rates varying from a few months in patients without a treatable driver mutation who do not respond to chemotherapy or immunotherapy to a few years in patients with a treatable driver mutation.[10, 11]

Earlier studies showed that patients are willing to undergo treatments that have limited benefits with major toxicity.[12] Furthermore, it is found that many patients mistakenly believe that their metastasized cancers are curable [13-16], or think that the goal/aim of the therapy they receive is cure. [15, 17, 18]

A few studies looked into patients' own treatment goals for starting a treatment for metastatic cancer. [19-21] Based on a pre-determined list of goals, Nipp et al. and El-Jawahri et al. found that 'extend my life as long as possible' (40% and 30%) and 'cure my cancer' (33% and 52%) were most often mentioned goals by patients with advanced lung cancer[19] and advanced gastro intestinal cancer.[19, 20] Rand et al. found similar results based on an open ended question about goals ('fight cancer' 52%, 'cure' 40%, 'live longer' 32%) for patients with advanced lung or gastro intestinal cancer and patients with melanoma.[21] In this study they also asked about feasibility of goals and found that 66% of the patients thought that 'cure' was feasible and 85% thought that 'fight cancer' was feasible.[21]

We conducted a similar study into patients' treatment goals, and because our study is more recent, we were able to not only include patients receiving chemotherapy, but also include patients receiving more currently available immunotherapy and TKIs. The goals possibly differ between different treatment therapies. To our knowledge, no previous research has been undertaken that compared goals of treatment among oncologists to that of patients with metastasized lung cancer. Therefore, we additionally also asked the treating oncologists of included patients about their own treatment goals for their patients and compared patients' and oncologists' goals.

Our main objectives were to study (1) the treatment goals of both the metastasized lung cancer patients and their oncologists before the start of treatment, (2) the concordance between patients' and their oncologists' goals for the treatment, (3) feasibility of these

goals as regarded by the patients and their oncologists and (4) which patient and healthcare characteristics are associated with having certain treatment goals.

Methods

Study design and population

We conducted a prospective multicentre study in six hospitals across the Netherlands, one academic and five non-academic hospitals, between November 2016 and April 2018. We included patients diagnosed with metastatic lung cancer who started a systemic treatment (chemotherapy, immunotherapy or targeted therapy with tyrosine kinase inhibitors (TKIs)). Patients were allowed to participate multiple times for different lines of therapy. Patients and their prescribing oncologists filled out a questionnaire about their treatment goals and their estimated feasibility of these goals immediately after the treatment plan was decided. After analysing the questionnaires, we conducted additional interviews with a subset of 15 patients and 5 oncologists from the academic hospital to better understand what they wanted to achieve with their treatment goals and how they assessed feasibility.

Questionnaire study

Data collection

Patients were identified from clinic schedules by treating oncologists. An information letter was given to the patient by the oncology nurse after the oncologist had discussed the medical treatment with the patient. Patients were approached at their next scheduled visit; patients who agreed to participate completed the informed consent and the questionnaire, gave permission to their oncologist to also complete a questionnaire and agreed to have their medical records reviewed. The oncologists completed the questionnaires on their treatment goals for the patient independently from the patients. The questionnaires had open ended questions on the treatment goals and a scale from 0-10 to rate the feasibility of the goals (see Figure A, appendix). In this questionnaire, patients also filled out the validated EORTC-QLQ-C15 quality of life questionnaire.[22] Patient and/or treatment characteristics were retrieved from the questionnaire (level of education, marital status, religious views), or from medical records (age, gender, histology of the tumour, type of medical treatment, line of treatment, comorbidity, ECOG performance score (categorized in 0, 1 and 2 or more) and treatment limitations).

Data analysis

The open-ended question about treatment goals was coded. From a subset of questionnaires from patients (n=150) and oncologists (n=145), the mentioned goals were coded independently and subsequently compared by 4 research members (HRWP, BDO, AM, AB). Discrepancies were resolved through discussion until 100% agreement was achieved. The

remaining 116 questionnaires from patients and 115 from oncologists were coded by one researcher (AM) and discussed with the research team.

Statistical analyses were conducted using IBM SPSS statistics 22. Differences between the demographic characteristics of the study participants were tested with Analysis Of Variance (ANOVA) for the continuous variable age and with the chi-square test for dichotomous and nominal variables. Generalized Estimated Equation (GEE) was used to attain understanding of the association between patient and healthcare characteristics and the treatment goals. By using the oncologists as a subject variable, GEE avoids the cluster effect present in the commonly used logistic regression models. The dependent variables were the goals mentioned by patients or oncologists. These variable were dichotomized in goal: 'quality of life', 'decrease tumour size', 'life prolongation' and 'cure' mentioned (yes/no). The independent variables were patient and healthcare characteristics. Patient characteristics were age (≤60, 61-70, ≥71), sex (male/female), marital status (married/unmarried), educational level (low/middle/high), religious views (yes/no), presence of comorbidity (yes/no), histology of the tumour (SCLC, NSCLC with targetable driver mutation (NSCLC+), NSCLC without targetable driver mutation (NSCLC-)) and performance status (ECOG (Eastern Cooperative Oncology Group) score 0, 1, ≥2). When the performance status was described using the Karnofsky score, this was recoded into the ECOG score (90-100% = 0, 70-80%=1, 50-60% =2, 30-40%=3, 10-20%=4). Healthcare characteristics were type of medical treatment for metastatic lung cancer (chemotherapy/immunotherapy/TKIs), line of medical treatment (first, second, third and more) and hospital type (academic/non-academic). Each statistically significant variable in the univariate GEE analyses ($p<0.10$) was entered into a multivariate GEE model. The final model was derived using the backward selection method, with a P-value of <0.05 as considered statistically significant. Results of the GEE analyses are presented as odds ratios (ORs) and associated 95% confidence intervals (CIs).

Additional semi-structured qualitative interviews

In order to better understand patients' and oncologists' treatment goals and thoughts on feasibility, we did additional interviews with patients who received treatment in the academic hospital, and their treating oncologists. Patients were recruited using purposive sampling to ensure as much variation as possible in treatment goals, perceived feasibility, sex, age and type of treatment. A total of 17 patients were invited, 15 patients agreed to participate. All 5 oncologists from these patients were interviewed. All participants were contacted by telephone, informed by an information letter and gave written informed consent prior to the interview. Patients received a gift voucher for their participation. Transcripts were anonymized during transcription. Access to the data was limited to five researchers.

Data was collected from November 2018 until March 2019. All interviews were performed by one researcher (HTK). Interviews were held at the participants' home or at the academic hospital using a semi-structured interview guide (see Table A, appendix) and the questionnaire

filled out by the respondent. The length of the interviews varied between 40 and 70 minutes for patients and between 25 and 35 minutes for oncologists. All interviews were audio recorded and transcribed verbatim. Written summaries were sent by mail to participants for member check.

We followed the principles of thematic analysis.[23] Three transcripts were coded independently by three researchers (HRWP, BDO, HTK) using Atlas.ti 7 and thereafter discussed intensively. Subsequently, all remaining interviews were coded by HTK and codes were finally grouped in themes and discussed with other researchers (HRWP, BDO, AM, AB).

Ethics, consent and permission

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, the Netherlands (number NL57455.029.16). Both patients and oncologists gave written consent to participate in the study and agreed to have the patients' medical records reviewed.

Results

Sample characteristics

In total, 376 eligible patients with metastatic lung cancer were approached for this study. After the information letter and questionnaire were given, 266 patients signed informed consent and filled out the questionnaire (figure 1). All 23 treating oncologists of the 266 included patients were approached, agreed to participate and filled out their questionnaire for a total of 260 patients. In total, 110 patients were not included in the study because participating was too emotional for them, because they already died before filling out the questionnaire, or because they did not return the questionnaire. Patients who were not included were more often female, had a performance score of ≥2, started the treatment in the first line and were treated in a non-academic hospital (Table B, appendix). From the included 266 patients, 19 patients participated twice for different lines of therapy.

Included patients had an average age of 65 years. Patients were starting treatment with immunotherapy (47%), chemotherapy (36%) or targeted therapy with TKIs (17%) respectively. Most oncologists were male (56%) and younger than 51 years old (79%). Three quarters of the patients were included in an academic hospital (75%) (table 1).

Patients' and oncologists' goals when starting medical treatment

We categorized the goals patients and oncologists formulated in four main treatment goals: 'quality of life', 'decreased tumour size', 'life prolongation' and 'cure', and we had a small category 'other'. Answers referring to symptom relieve were categorized as 'quality of life',

and answers referring to fight cancer or stop cancer as 'decreasing tumour size'. See table C in the appendix for all codes and categories.

Patients reported 1,5 treatment goals on average [range: 1-4]. Overall, 45% of patients (n=119) reported 'quality of life', 45% reported 'life prolongation' as a treatment goal, 39% reported 'decrease in tumour size' (n=103) and 19% reported 'cure' (n=50).

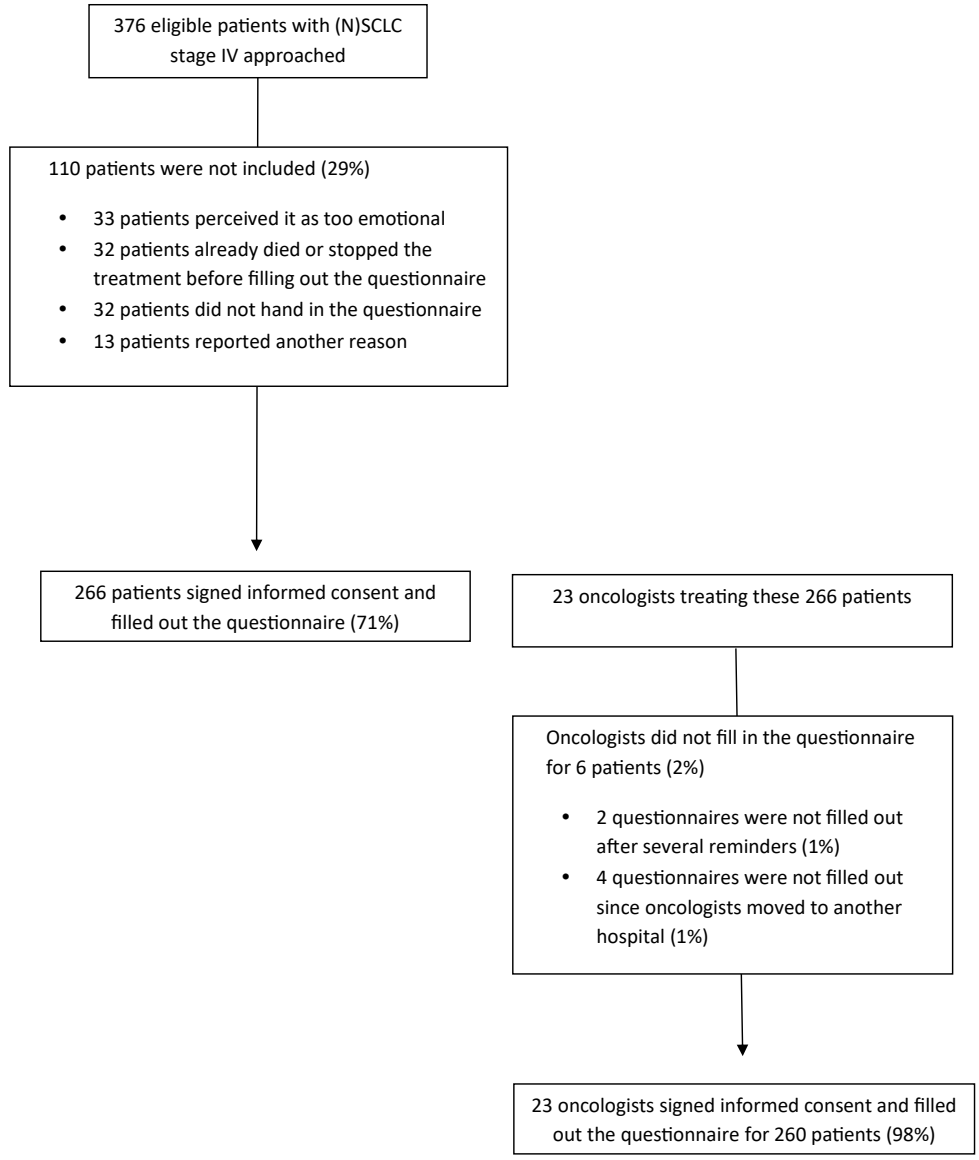

Figure 1. Flowchart recruitment of patients and oncologists

Table 1. Demographic characteristics of study participants (n=266)

Variable	Chemotherapy	Immunotherapy	TKIs	Total
	N=96 (36%)	N=126 (47%)	N=44 (17%)	N=266 (100%)
Age – Years (mean ± SD)	65±9	65±9	66±11	65±9
Sex				
Male	57 (59)	68 (54)	20 (45)	145 (55)
Female	39 (41)	58 (46)	24 (55)	121 (45)
Marital status				
Married	77 (80)	94 (75)	33 (75)	204 (77)
Unmarried	19 (20)	32 (25)	11 (25)	62 (23)
Education *				
Low	16 (19)	29 (28)	10 (26)	55 (24)
Middle	48 (56)	46 (44)	13 (34)	107 (47)
High	22 (25)	30 (28)	15 (40)	67 (29)
Religious views				
Yes	37 (38)	46 (36)	22 (50)	105 (39)
No	59 (62)	80 (64)	22 (50)	161 (61)
Comorbidity *				
Yes	63 (68)	86 (70)	23 (56)	172 (67)
No	31 (32)	37 (30)	18 (44)	86 (33)
ECOG performance score *				
0	21 (27)	21 (17)	11 (26)	53 (22)
1	43 (55)	75 (62)	22 (53)	140 (58)
≥ 2	14 (18)	27 (21)	9 (21)	49 (20)
Tumour histology				
SCLC	13 (14)	0	0 (0)	13 (5)
NSCLC with targetable driver mutation	19 (20)	11 (8)	41 (93)	71 (27)
NSCLC without targetable driver mutation	64 (67)	115 (91)	3 (7)	182 (68)
Line of treatment				
1st	60 (62)	34 (27)	17 (39)	111 (42)
2nd	20 (21)	79 (63)	14 (32)	113 (43)
≥ 3rd	16 (17)	13 (10)	13 (29)	42 (15)
Hospital type				
Academic	48 (50)	115 (91)	37 (84)	200 (75)
Non-academic	48 (50)	11 (9)	7 (16)	66 (25)
Sex oncologist (n=260)				
Male	48 (51)	61 (49)	39 (89)	148 (56)
Female	47 (49)	64 (51)	5 (11)	116 (44)
Age oncologist (n=260)				
< 40	25 (26)	61 (49)	19 (43)	105 (40)
41-50	51 (54)	43 (34)	9 (21)	103 (39)
≥ 51	19 (20)	21 (16)	16 (36)	56 (21)

TKI: tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC-: NSCLC without targetable driver mutation; NSCLC+: NSCLC with targetable driver mutation.

* Denotes missing of; education: 14%, comorbidity: 3%, ECOG performance score: 9%

Patients who received chemotherapy or immunotherapy most often reported the goal 'life prolongation' (52% and 40% respectively). Most patients who received TKIs mentioned 'quality of life' (55%) (figure 2A).

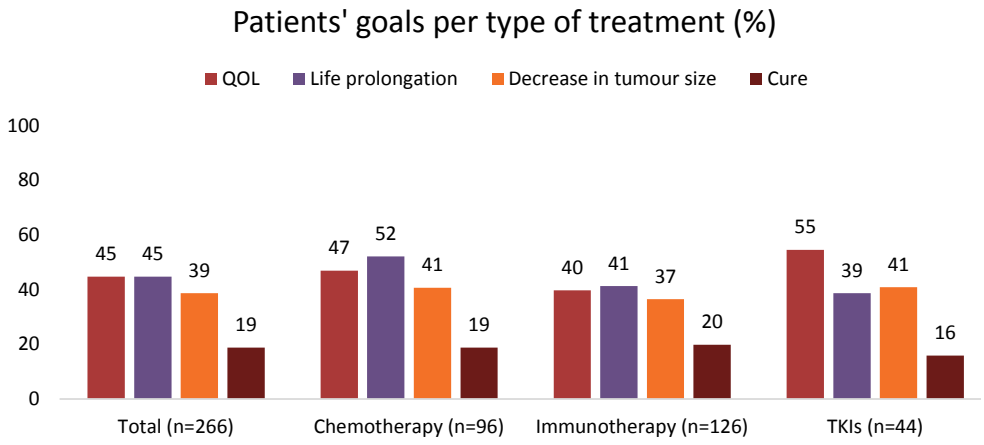

Figure 2A. Goals of patients categorized per type of treatment

Oncologists reported 1,9 treatment goals on average for a total of 260 patients [range: 1-4]. For participating oncologists, 72% reported 'quality of life' (n=186) as a treatment goal, 66% 'decrease in tumour size' (n=171), 55% 'life prolongation' (n=142), and 2% 'cure' (n=5). Oncologists reported 'quality of life' most often for each treatment type (68%, 68% and 80%) (figure 2B).

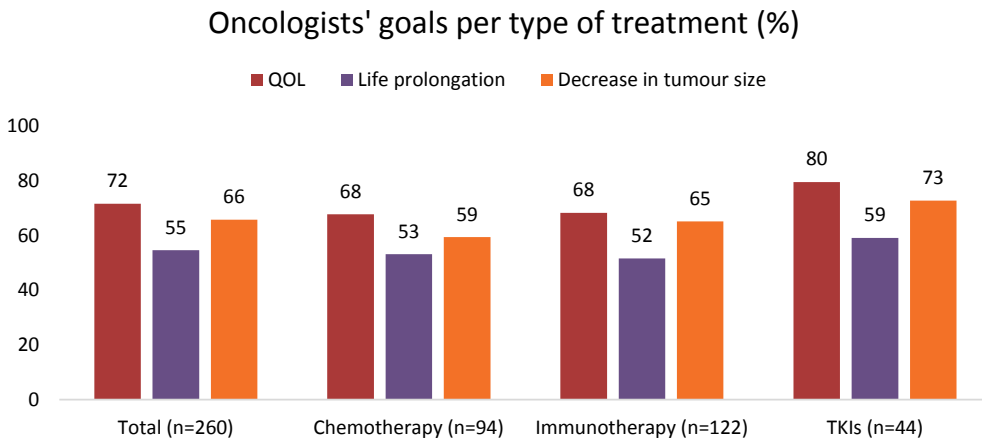

Figure 2B. Goals of oncologists categorized per type of treatment

Concordance and discussion of treatment goals

Concordance between patients' and oncologists' treatment goals was overall low. Concordance was highest for the goal 'quality of life' (33%), followed by 'life prolongation' (27%) and 'decrease in tumour size' (24%) (figure 2C). A lower performance status was associated with a higher concordance between patients' and oncologists' goals (OR=2.321;95%CI=1.135-4.744) (table D, in appendix).

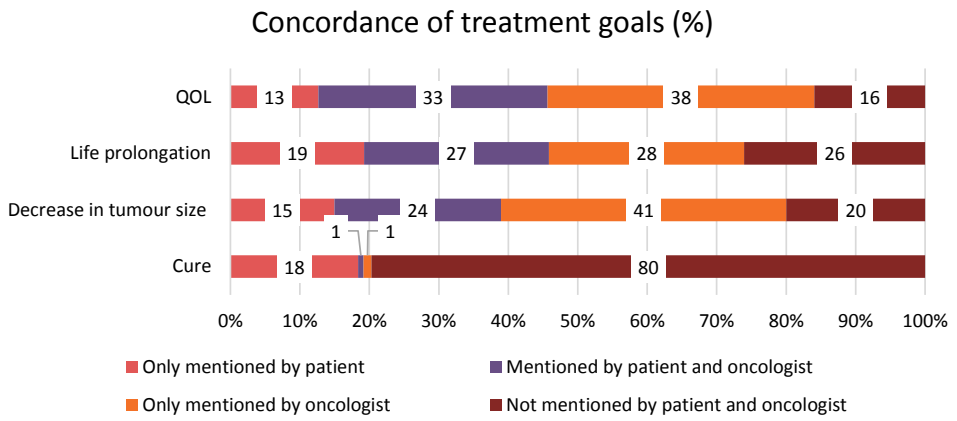

Figure 2C. Concordance between patients' and oncologists' treatment goals (n=260)

Patients reported that they discussed their treatment goals in 82% of the cases with their oncologists and in 88% with their family. Oncologists reported that they discussed their treatment goals in 91% of the cases with the patient.

Expected feasibility of treatment goals

Patients reported an average feasibility for their treatment goals (in mean ± SD) of 6.8 ± 1.6 (figure 3). Since patients reported all their goals with one score on feasibility, we could only analyse the feasibility per goal only when one goal was reported (n=134). These patients reported an average SD) feasibility of 6.0 ± 1.3 for 'quality of life' (n=24), 6.8 ± 1.6 for 'decrease in tumour size' (n=42), 7.3 ± 1.4 for 'life prolongation' (n=41) and 7.0 ± 1.8 for 'cure' (n=27) (Figure A, appendix).

Oncologists reported a lower average feasibility for their treatment goals of 5.8 ± 2.1 (mean ± SD) (figure 3). Their mean feasibility scores (shown in mean ± SD) were 6.1 ± 2.0 for 'quality of life' (n=186), 5.5 ± 2.1 for 'decrease in tumour size' (n=171), 5.7 ± 2.2 for 'life prolongation'(n=142) and 2.6 ± 1.8 for 'cure' (n=5) (Figure B, appendix).

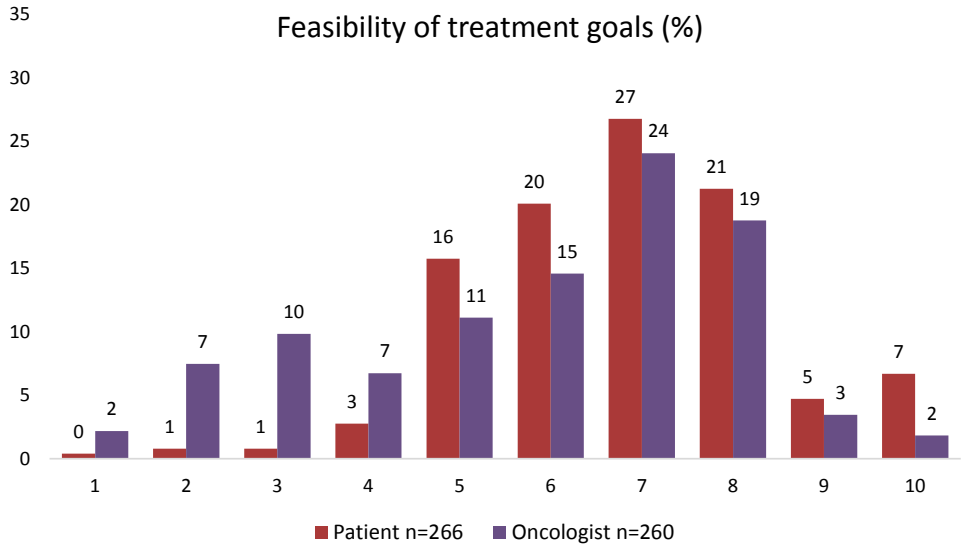

Figure 3. Feasibility of treatment goals according to patients and oncologists. Missing of; patients: 5%, oncologists: 3%

Patient and care characteristics associated with treatment goals

For patient goals, the goal 'quality of life' was associated with patients being older, having a high educational level and having a lower performance status. The goal 'life prolongation' was associated with patients being married and patients without religious views. 'Life prolongation' was mentioned significantly less often by patients who started immunotherapy or TKIs, compared to patients who started chemotherapy. The goal 'decrease in tumour size' was associated with patients being younger and patients having a higher educational level. The goal 'cure' was associated with patients having a lower educational level and patients with religious views (Table 2).

Oncologists reported the goal 'quality of life' less often when patients had a middle educational level compared to patients with a low educational level. The goal 'life prolongation' was reported more often by oncologists for patients having a higher educational level. The goal 'decrease in tumour size' was more often reported by oncologists when patients had no religious views and when patients were diagnosed with NSCLC, without or with a targetable driver mutation (Table 2).

Further insight in treatments goals and feasibility scores

Setting goals like 'cure' or 'life prolongation' was mentioned by several patients in the additional interviews as an expression of willpower to stay alive and non-acceptance of dying. Besides this, goals often were given in order to seize chances for improvement and to actively 'fight the fight' as best as they could, 'doing everything' or 'doing something' (Table 3, Q1).

Table 2. Multivariate GEE analyses of factors associated with patients' and oncologists' treatment goals

Patient	Quality of life		Life prolongation		Decrease in tumour size		Cure	
Patients. N=266 Variable (N)	**Goal present (row %)**	**Multivariate OR (95%-CI)**	**Goal present (row %)**	**Multivariate OR (95%-CI)**	**Goal present (row %)**	**Multivariate OR (95%-CI)**	**Goal present (row %)**	**Multivariate OR (95%-CI)**
Age–Years								
≤60 (78)	37	1.0			51	**3.27 (1.23 – 8.72)**		
61-70 (111)	41	1.18 (0.53 – 2.59)			37	1.99 (0.88 – 4.46)		
≥71 (77)	55	**1.87 (1.06 – 3.30)**			29	1.0		
Marital status								
Married (204)			49	**2.62 (1.52 – 4.53)**				
Unmarried (62)			29	1.0				
Education								
Low (55)	33	1.0			36	1.0	20	**6.66 (1.64 – 26.99)**
Middle (107)	45	1.57 (0.89 – 2.75)			32	0.86 (0.36 – 2.03)	23	**7.30 (3.02 – 17.65)**
High (67)	54	**2.17 (1.03 – 4.59)**			61	**3.00 (1.01 – 8.88)**	5	1.0
Religious views								
Yes (105)			31	1.0			25	**2.36 (1.15 – 4.85)**
No (161)			52	**2.57 (1.65 – 4.01)**			14	1.0
ECOG performance score								
0 (53)	30	1.0						
1 (140)	45	**2.17 (1.19 – 3.99)**						
≥ 2 (49)	55	**3.06 (1.58 – 5.95)**						
Type of medical treatment								
Chemotherapy (96)			51	1.0				
Immunotherapy (126)			41	**0.58 (0.42 – 0.80)**				
TKIs (44)			39	**0.65 (0.42 – 1.00)**				
Oncologists. N=260								
Education								
Low (54)	76	1.0	48	1.0				
Middle (105)	64	**0.56 (0.33 – 0.96)**	54	1.37 (0.75 – 2.49)				
High (64)	83	1.53 (0.72 – 3.23)	64	**1.75 (1.18 – 2.96)**				
Religious								
Yes (103)					56	1.0		
No (157)					72	**2.35 (1.56 – 3.54)**		

Continue

Continued

Patient	Quality of life		Life prolongation		Decrease in tumour size		Cure	
Patients. N=266 Variable (N)	**Goal present (row %)**	**Multivariate OR (95%-CI)**	**Goal present (row %)**	**Multivariate OR (95%-CI)**	**Goal present (row %)**	**Multivariate OR (95%-CI)**	**Goal present (row %)**	**Multivariate OR (95%-CI)**
Tumour histology								
SCLC (13)					31	1.0		
NSCLC- (177)					66	**5.01 (1.34 – 18.69)**		
NSCLC+ (70)					73	**8.34 (1.60 – 43.64)**		

All variables were entered in the univariate model (age, sex, marital status, educational level, religious views, presence of comorbidity, histology of the tumour, performance status, type of medical treatment, line of medical treatment and hospital type), only significant multivariate variables are shown in bold (with a p-value of ≤0.05). OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; TKI: Tyrosine Kinase Inhibitor; SCLC: small cell lung cancer; NSCLC-: NSCLC without targetable driver mutation; NSCLC+: NSCLC with targetable driver mutation

Table 3. Quotes of patients and oncologists on reasons for setting treatment goals and feasibility scores

No	*Quotes of patients*
Q1	*"And not only [not giving up] for yourself, but also for the people surrounding you. But resign yourself, that doesn't help anyone. No treatment feels like giving up, like, what do I care. Yes, you try everything to… You see, if it didn't work, I wouldn't be so lucky but at least I tried. It is all about doing something." (P26, female, age 72, talking about treatment goal 'the best quality of life')*
Q2	*"And I can try to cure. There is a chance. There will always be a chance. And I try to take that chance. I grab all chances I get. I grab everything I can. Nothing is out of my league. And one person is not the other one. One person will get very sick, the other one will think: I won't get sick. Yes, that is the thing with chemotherapy, some people get really sick." (P134, , female, age 55, talking about treatment goals 'to stop the cancer', to stop the tumour', 'that specialists might learn from this')*
Q3	*"Sometimes I feel like, well, I don't want to be the biggest optimist, but I always think that one can be helped, you never know. Today they have nothing for you but maybe tomorrow there will be something. And that is what I try to think. It is hope, hope that there might be something. You always have to keep hope, otherwise you can better start arranging your funeral." (P168, male, age 59, talking about treatment goals 'to rather be better' and 'to prolong life')*
Q4	*"You keep in mind that the eternal live, or let's say, until your ninety's, that might be unrealistic. But at least, maybe one extra year. So one extra year might be a 5 and (to live) until your 99th might be a 10. Yes, and then something in between. The [feasibility score] is kind of hope. I hope that it is as long as possible." (P175, male, age 64, talking about feasibility score of 7)*
No	*Quotes of oncologists*
Q5	*"I: You just mentioned, maybe that this patient might live a bit longer, that the symptoms might be delayed, but I don't see that goal on your questionnaire. P: No, I indeed mentioned symptom delay and the question is if that is in line. Most of the time it goes hand in hand. People get complaints because they have feelings of nausea, have fever, they might die from that. But for her it is about symptom delay I think. Living a couple of months longer will for her be.." (O4, oncologist, female, talking about treatment goals 'delay symptoms and 'decrease tumour growth')*
Q6	*"There is always a small chance that it might work. If you don't do anything, you know you will die. And if you than say, I want to grab that opportunity, I think you should just do it, even though it might not be the right candidate. If it does work, you are on the winning hand so to speak. And now (without starting treatment) you might be losing." (O5, oncologist, female, talking about treatment goal 'decrease tumour growth')*
Q7	*"I have the experience with patients by whom it also started like this and that it eventually goes well. That is the drive, in the end. I have the experience that there are many people who feel better with immunotherapy and also live longer for 2 years with a good quality of life. Up front it is not always easy to see if that is the person in front of you. So than you think, well we can at least try, otherwise they will most certainly die and this treatment is not very burdensome. It is an consideration, yes and people really want to get the chance." (O4, oncologist, female, talking about feasibility score of 6 for goal 'to improve quality of life')*

Also, patients explained they set treatment goals while realizing that the chances for achieving them were small. But they wanted to take any chance (Table 3, Q2).

Patients explained that setting positive treatment goals gave them hope for cure, life prolongation or decrease of tumour size which made the disease process more bearable. It made patients feel better and functioned as a reason to stay optimistic (Table 3, Q3). Patients explained the feasibility scores that they attributed to their goals as an expression of the hope for good results (Table 3, Q4). This hope was not so much based on known chances on success, but more on oncologists' willingness to start treatment and examples of patients who responded well to treatment.

All oncologists mentioned that their treatments were intended as palliative treatments. When specifically speaking in terms of palliative treatment, they aimed at symptom relief, a good quality of life or preventing future symptoms. Life prolongation could then possibly be a side effect (Table 3, Q5). Besides, interviewed oncologists explained that they did not set cure as a goal, because this was not realistic; life prolongation and decrease in tumour size were the highest achievable goals. Treatment was perceived by oncologists as the only chance to achieve life prolongation. They did not want to miss chances for improvement of the patients' situation, despite small chances for treatment success (Table 3, Q6). No treatment or, in interviewed oncologists' words 'doing nothing' was therefore not an option. Oncologists mentioned that estimating feasibility of treatment goals is often difficult. Examples of unexpected successful results of treatment in former patients, was a reason to set relatively high feasibility scores (Table 3, Q7).

Discussion

Patients and oncologists reported 'quality of life' (45%;72%), 'life prolongation' (45%;55%), 'decrease in tumour size' (39%;66%) and 'cure' (19%;2%) as treatment goals respectively. Patients who received chemotherapy most often reported 'life prolongation' as a goal. Most patients who received TKIs reported 'quality of life' as a goal. Oncologists reported 'quality of life' most often for every treatment type. Concordances between patients' and oncologists' treatment were low: highest for 'quality of life' (33%), followed by 'life prolongation' (27%) and 'decrease in tumour size' (24%). Patients had slightly higher feasibility scores than oncologists (6.8 vs 5.8 on a 10-point scale). More than known success rates, examples of patients where it went unexpectedly well and hope seem to influence the goal setting and feasibility score. Educational level, age, religious views and performance status of patients were associated with certain treatment goals.

The percentages of patient treatment goals that we found in our study are partly comparable with results of Rand et al., who looked at priority goals in patients with advanced lung cancer, advanced gastro intestinal cancer and melanoma.[21] We found higher percentages for the treatment goals 'life prolongation' (45% compared to 32% 'live longer' as treatment goal found by Rand et al.) and 'quality of life' (45%, compared to 30% 'comfort' as treatment goal found by Rand et al.) and lower percentages for the treatment goal 'decrease tumour growth' (including fight cancer) (39%), compared to 52% 'fight cancer' as treatment goal found by Rand et al.[21] There is the greatest difference in percentage of patients having 'cure' as treatment goal (19% in our study compared to 40% in the study of Rand et al.).[21] Our findings are less comparable with results of Nipp et al. and El-Jawahri et al., who asked patients with advanced lung cancer and advanced gastro intestinal cancer for (only) one treatment goal (out of a list of possible treatment goals). They found 'cure' (33% and 52%), 'extend life as long as possible' (40% and 30) and 'lessen my suffering' (quality of life) (4% and 4%) as treatment goals respectively.[19, 20]

The differences found between the studies might be the result of different research methods, but it might also be the result of cultural differences. For the Netherlands it has been found that physicians and patients are relatively open in communicating prognosis; this might explain the relatively low percentages for 'cure' as treatment goal that we found.[24]
We didn't find studies on the treatment goals oncologists have when starting a treatment specifically for metastatic lung cancer.

Cure is the most difficult goal to understand, as all patients were in the advanced stages of a disease. From the interviews it appeared that hope can play an important role in setting this goal, which suggests that patients do not necessarily see it as a realistic goal. Rand et al. concluded that patients hold optimistic expectations for achieving their goals and for surviving.[21] Setting 'cure' as a treatment goal might therefore be a coping strategy for patients dealing with an incurable disease. However it can also be that patients misunderstood that they could be cured, as found in previous studies. [13-16, 18, 25] We found an association between lower educational level and the treatment goal 'cure'. This might mean that patients with a lower educational level more often think their cancer may be cured. This finding highlights the importance of clear communication between oncologists and patients.

The questionnaire study showed that – apart from cure of which they know it is not realistic- oncologists least often mentioned life-prolongation as goal; over half of oncologists mentioned it. Above that the qualitative study showed that the oncologists generally saw this goal more as a side effect of goals related to quality of life and treatment of burdensome symptoms. This suggests that they foremost have a palliative intent with starting treatment. At the same time they seem to describe the option of not giving systemic treatment as giving no treatment or doing nothing, while both patients and oncologists feel they do need to do something,

probably because of not wanting to be abandoned by the physician or abandon the patient. Introducing palliative care as an option to relieve symptoms and achieve the best possible quality of life can therefore be beneficial.

Although patients reported that they discussed their treatment goals in 82% of the cases with their oncologists and oncologists in 91% of the cases with the patient, we found overall low concordances between patients' and oncologists' goals: between 24% for 'decrease in tumour growth' and 37% for 'quality of life'. A recent study by Almalki et al. found that only 13.7% of patients had full concordance with their physicians regarding the aspects of their treatment plans. However, this study consisted of a heterogeneous cancer population.[26] Douglas et al. showed that 23.3% of patients with advanced cancer and their oncologist had strong goal of care agreement for 'survival' (8.3%) or 'quality of life' (15%).[27] In a South-Korean study they found that the agreement rates between cancer patients and oncologists was 69% for treatment goal.[28] Having a low performance status was related to higher concordance. Possibly in these cases it is clearer which goals can still be strived for.

The concordance was especially low for the goal 'decrease tumour size'. The interviews with oncologists showed that with their direct goal of decrease tumour size, they wanted to achieve a more ultimate goal, for instance delaying symptoms (Q5 in table 3). It is possible that an oncologist puts emphasis on the direct goal in the questionnaire and more emphasis on the ultimate goals in the discussion with the patient (or vice versa). In such cases non-concordance between patients' and oncologists' treatment goals might be an artefact. Another explanation might be that patients misunderstood what the oncologist communicated. Chou et al. concluded that the oncologists' language may obscure discussions of (prognosis and) treatment goals. They observed that oncologists can use complex language, medical jargon, modal expressions (indirectness) and euphemisms in their conversations with patients with advanced cancer.[29] Using 'decrease tumour size' instead of what they want to achieve with this decrease – increased quality of life or life-prolongation–can be seen as an example of this. However, it might also be that patients and oncologists actually had different goals, without misunderstanding; in those cases non-concordance is logical. Nevertheless, discussing patients' treatment goals is part of high-quality care, allowing physicians to align treatments with what is most important and realistic to the patient.[30, 31]

Feasibility scores for different goals differed for patients and oncologists, with patients giving slightly higher scores. From the interviews it appeared that most patients mentioned 'hope' as an explanation for a high feasibility score before treatment. This might also explain the rather high feasibility score of 7,0 for 'cure'. It became clear that oncologists can also have an influence on this 'hope'. Their willingness to start a treatment fed patients' hope for a cure or for life prolongation as seen in the interviews. Rand et al. found a similar feasibility score for 'cure' (6,6) and a higher score for 'fight cancer' (8,4, compared to 6,8 we found for 'decrease

tumour growth').[21] Oncologists mentioned that it is difficult to determine feasibility scores, but that they took into account the chance that the treatment could be beneficial or could have unexpected results.

Strengths and limitations

Strengths of this study are the large sample size of patients, the contribution of both one academic and five non-academic hospitals, the use of open ended questions, so that patients and oncologists had to formulate goals in their own words and the additional semi-structured interviews to better understand respondents answers. A limitation is that we only interviewed patients and oncologists from the academic hospital, possibly giving bias to the additional information since this may be a different kind of patient population wherein more treatment lines and new therapies are available and patients might be more willing 'to try everything'.

Conclusion and implications

Patients and oncologists set various goals for the treatment they receive/prescribe. There are no relevant differences in the treatment goals between chemotherapy, immunotherapy or targeted therapy. Concordance between patients' and oncologists' goals is low. This might be because they actually have different goals, but it might also be the result of the patient misunderstanding the effectiveness or side effects of treatments. Patient characteristics, such as age and educational level can play a role in this, but also suboptimal communication of the oncologist. It is important that the oncologist informs patients and their families clearly about the feasibility of their treatment goals and help them to make decisions that best suit their preferences. As patients can only make a well-considered decision if they are adequately informed, clear communication about treatment goals should be integrated into clinical care. This communication should include the option of palliative care. Attention for this in education and training of oncologists can help with achieving this. Following the principles of shared decision making would be appropriate in such a training.[32] Also making use of a decision aid can be helpful.[33]

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APPENDIX

Questionnaire for patients:

- "*What are your goals with this treatment*?"

1._____

2._____

3._____

4._____

5._____

- "*Did you discuss these goals with your oncologist / family*?"

Oncologist: Yes/no

Family: Yes/no

- "*To what extent do you think these goals are feasible*?"

0 1 2 3 4 5 6 7 8 9 10
not feasible at all highly feasible

Questionnaire for oncologists:

- "*Who made the treatment decision*?"

  The patient wanted this treatment

  I decided for this treatment

  The patient and I decided together

- "*What are your goals with this treatment*?"

1._____

2._____

3._____

4._____

- "*Did you discuss these goals with the patient*?"

1. Yes/no
2. Yes/no
3. Yes/no
4. Yes/no

- "*To what extent do you think these goals are feasible*?"

1. 0 1 2 3 4 5 6 7 8 9 10
2. 0 1 2 3 4 5 6 7 8 9 10
3. 0 1 2 3 4 5 6 7 8 9 10
4. 0 1 2 3 4 5 6 7 8 9 10

not feasible at all highly feasible

Figure A. Questionnaires for patients and oncologists

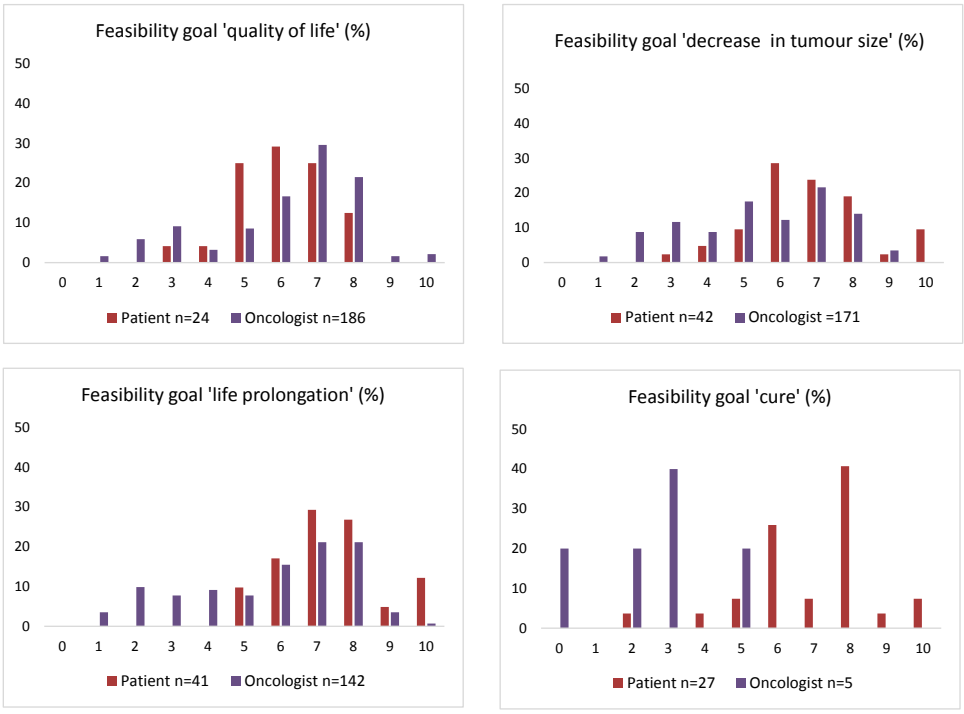

Figure B. Feasibility of treatment goals according to patients and oncologists. Note: feasibility score of patients reporting one goal

Table A. Interview guide for semi-structured interviews with patients and oncologists

Interview guide for semi-structured interviews with patients	Interview guide for semi-structured interviews with oncologists

• Introducing the subjects, aim of the interview
• Bringing up previously completed questionnaires before and after treatment
• Informed consent and audio recording
• Introductory question: asking the participant how he/she lately experienced health and illness
• Preparation of treatment choice and treatment goals
  ◦ Important values for the patient
  ◦ Reason for setting mentioned goals (e.g. cure)
  ◦ Discussing goals with the oncologist
  ◦ No treatment as an option
• Achieved goals
  ◦ Explanation of score at goal achieved / not achieved
  ◦ Explanation of satisfaction when goals are (not) achieved
  ◦ Explanation of score at quality of life
• Evaluation afterwards
  ◦ Do the same / differently afterwards (e.g. preparation)
  ◦ Advices for oncologists
• Verbal summary and member check
• Gift voucher
	• Introducing the subjects, aim of the interview
	• Bringing up previously completed questionnaires before and after treatment
	• Informed consent and audio recording
	• Introductory question: asking the participant how he/she remembers the patients
	• Reasons for setting mentioned goals (e.g. survival)
	  ◦ Underlying explanation of mentioning these goals in terms of achievement
	  ◦ Used terms regarding
	  ◦ Discussing goals with the oncologist
	  ◦ No treatment as an option
	• Achieved goals
	  ◦ Explanation of score at goal achieved / not achieved
	  ◦ Explanation of satisfaction when goals are (not) achieved
	  ◦ Explanation of score at quality of life
	• Evaluation afterwards
	  ◦ Do the same / differently afterwards (e.g. preparation)
	  ◦ Advices for oncologists
	• Verbal summary and member check
	• Gift voucher

Table B. Comparison of included and not included patients

N=376 Variable (N)	**Patients who were included (column %)**	**Patients who were not included (column %)**	**p-value**
Age in years			
<60 (107)	30	26	
61-70 (151)	41	38	
≥ 71 (116)	29	36	0.392
Sex			
Male (188)	55	40	
Female (186)	45	**60**	**0.010**
Marital status			
Married (267)	77	72	
Unmarried (86)	23	28	0.420
Comorbidity			
Yes (246)	67	72	
No (115)	33	28	0.314
ECOG performance score			
0 (65)	22	14	
1 (184)	58	53	
≥ 2 (77)	24	**33**	**0.039**
Tumour histology			
SCLC (21)	5	8	
NSCLC without targetable driver mutation (258)	68	71	
NSCLC with targetable driver mutation (92)	27	21	0.344
Type of medical treatment			
Chemotherapy (143)	36	44	
Immunotherapy (167)	47	39	
TKIs (62)	17	17	0.253
Line of treatment			
1st (178)	41	**63**	
2nd (142)	43	28	
≥ 3rd (51)	16	9	**0.001**
Hospital type			
Academic (271)	75	65	
Non-academic (105)	25	**35**	**0.036**

ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.05.

Table C. Examples of treatment goals from patients and oncologists

Category	**English**
Quality of life	Having a more comfortable life
	Better quality of life
	Better mobility
	Feeling better
	Being able to do more things than I can do now
	The best quality of life
	Making the quality of life as high as possible
	Having a bearable life
	Having a pleasant life
	Good quality of life
	Quality of life
	Improve quality of life
	Improve life
	Strive for a better life than I have now
	Living life to the fullest
	Pain relieve
	Improvement
	Improve life circumstances
	Relieve dyspnoea
	Less symptoms
	More oxygen
	Less pleural effusion
	Being less ill
Decrease in tumour size	Decrease tumour carcinoma
	Slow down tumour
	Slow down metastases
	Restriction of tumours
	To stop cancer cells from growing
	To stop the cancer
	To prevent the cancer from growing
	To control cancer
	That the cancer disappears
	To decrease the tumour cells
	That the tumour disappears
	That it does not grow any further
	High stabilization of the disease
	To fight the cancer
	Prevent new metastases
	To stop the tumour from growing
	To delay the cancer process
	To stop the cancer
	Stopping the disease process
	To shrink the tumour
	To slow down the disease
	To slow down the cells

Continue

Continued

Category	**English**
	Staying stable
	Stop the cancer
	To withhold the tumour
	To shrink the tumour
	To delay the growth
Life prolongation	Better life opportunities
	To live longer
	To enjoy time with my partner as long as possible
	A future
	Extra time
	To live longer
	Longer lifespan
	To prolong life
	Life prolongation
	More time
	To live as long as possible
	Time gain
	Postpone death
	To prolong life
Cure	Getting better
	That I recover
	Cured
	Recovery
	Regain one's health
	Prefer speedy recovery
	Gain health
Other	Visiting Suriname
	Nothing
	To keep the option for radiation
	To quit
	To do everything about it
	Improve medication for future patients
	To contribute to science
	So that specialists can learn
	To have the feeling I have tried everything
	Gain more insight in research
	To keep the option for immunotherapy

Table D. Univariate GEE analyses of factors associated with concordance between treatment goals of patient and oncologist

N=266 Variable (N)	**Concordance between treatment goals (row %)**	**Univariate OR (95%-CI)**	**p-value**
Age in years			
≤60 (78)	59	1.0	
61-70 (111)	66	1.199 (0.560 – 2.567)	0.641
≥71 (77)	70	1.464 (0.718 – 2.988)	0.295
Sex			
Male (145)	68	1.351 (0.830 – 2.198)	0.226
Female (121)	62	1.0	
Marital status			
Married (204)	68	1.650 (0.751 – 3.628)	0.212
Unmarried (62)	55	1.0	
Education			
Low (55)	64	1.0	
Middle (107)	63	0.894 (0.475 – 1.683)	0.728
High (67)	75	1.790 (0.694 – 4.612)	0.228
Religious			
Yes (105)	63	1.0	
No (161)	67	1.186 (0.714 – 1.970)	0.510
Comorbidity			
Yes (172)	66	1.423 (0.965 – 2.099)	0.075
No (86)	61	1.0	
ECOG performance score			
0 (53)	53	1.0	
1 (140)	66	1.797 (0.777 – 4.159)	0.171
≥ 2 (49)	74	2.321 (1.135 – 4.744)	**0.021***
Tumour histology			
SCLC (13)	69	1.0	
NSCLC without targetable driver mutation (182)	63	0.834 (0.417 – 1.667)	0.607
NSCLC with targetable driver mutation (71)	69	1.068 (0.255 – 4.475)	0.928
Type of medical treatment			
Chemotherapy (96)	69	1.0	
Immunotherapy (126)	59	0.637 (0.314 – 1.291)	0.211
TKIs (44)	75	1.199 (0.653 – 2.203)	0.558
Line of treatment			
1st (111)	69	1.0	
2nd (113)	64	0.875 (0.539 – 1.420)	0.589
≥ 3rd (42)	60	0.679 (0.211 – 2.182)	0.515
Hospital type			
Academic (200)	66	1.082 (0.523 -2.238)	0.833
Non-academic (66)	64	1.0	

OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors
*p value ≤ 0.05

5

PATIENTS WITH METASTATIC LUNG CANCER AND ONCOLOGISTS VIEWS ON ACHIEVEMENT OF TREATMENT GOALS AND MAKING THE RIGHT TREATMENT DECISION: A PROSPECTIVE MULTICENTRE STUDY

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Abstract

Objective: Previous studies have investigated patients' treatment goals before starting a treatment for metastatic lung cancer. Data on the evaluation of treatment goals are lacking.

Aim: To determine if patients with metastatic lung cancer and their oncologists perceive the treatment goals they defined at the start of systemic treatment as achieved after treatment and if in hindsight they believe it was the right decision to start systemic therapy.

Methods: A prospective multicentre study in six hospitals across the Netherlands between 2016 and 2018. Following systemic treatment, 146 patients with metastatic lung cancer and 23 oncologists completed a questionnaire on the achievement of their treatment goals and whether they made the right treatment decision. Additional interviews with 15 patients and 5 oncologists were conducted.

Results: According to patients and oncologists, treatment goals were achieved in 30% and 37% for 'quality of life', 49% and 41% for 'life prolongation', 26% and 44% for 'decrease in tumour size' and 44% for 'cure' respectively. Most patients and oncologists, in hindsight, felt they had made the right decision to start treatment, also if they had not achieved their goals (72% and 93%). This was related to the feeling that they had to do 'something'.

Conclusion: Before deciding on treatment, the treatment options, including their benefits and side-effects, and the goals patients have, should be discussed. It is key that these discussions include not only systemic treatment, but palliative care as effective options for doing 'something'.

Introduction

Lung cancer is the most frequent cause of cancer-related deaths worldwide.[1] In the Netherlands, over 14,000 patients are diagnosed with lung cancer each year.[2] Lung cancer is mostly diagnosed in an advanced stage since earlier stage disease may not always cause disease specific symptoms.[2] At time of presentation, lung cancer frequently has an aggressive course of disease, even with systemic treatment.[3]

Systemic treatments such as chemotherapy, targeted therapy with tyrosine kinase inhibitors (TKIs) and immunotherapy are often initiated in patients with metastasized lung cancer despite the aggressive course, the incurability and the possible side effects.[4-10]

Previous studies have looked into treatment goals patients have when starting systemic treatment for metastatic lung cancer. Goals that were mostly mentioned by patients in these studies are 'quality of life', 'life prolongation', 'decrease of tumour growth' and 'cure'.[10-13]

Data on the evaluation of treatment goals are lacking. To what extent do patients and oncologists perceive their goals as achieved after treatment, and do they, in hindsight, think it was the right decision to start systemic therapy? Insight from this evaluation can help future patients and oncologists to make the decision about whether or not to start systemic treatment. The main objectives of this study were, from the perspective of patients and oncologists separately, to determine (1) the percentage that achieved treatment goals as defined at the start of treatment, (2) which characteristics of patients and healthcare were associated with achievement of treatment goals and (3) whether, in hindsight, it was the right decision to start the treatment.

Methods

Study design and population

We conducted a prospective multicentre study in six hospitals (one academic and five non-academic) across the Netherlands between November 2016 and April 2018. We included patients diagnosed with metastatic lung cancer who started a systemic treatment (chemotherapy, immunotherapy or targeted therapy with TKIs) as part of usual care. Patients and their oncologists received a questionnaire on their treatment goals after the treatment regime was discussed between the patient and their oncologist and before the start of systemic treatment. Within two weeks after the agreed upon systemic treatment was completed the patients received a questionnaire about the achievement of the treatment goals they had defined at the start of treatment and whether, in hindsight, they felt starting the treatment had been the right decision. The study team was aware of this moment of completion of treatment (this could be within weeks or within months) due to weekly multidisciplinary team meetings where treatment of all metastatic lung cancer patients were discussed. After analyses, we felt the need to better understand respondent answers, e.g.

considering starting the treatment to be the right decision even if stated treatment goals were not achieved. Therefore, we conducted additional qualitative interviews with a subset of patients and oncologists. For reasons of feasibility we limited these interviews to patients of an academic hospital. We considered this possible because we did not find differences in achieving goals according to patients and oncologists between academic and non-academic hospitals.

Questionnaire study

Data collection

Patients completed the informed consent and gave permission for their oncologist to complete their questionnaires and to have their medical records reviewed. The patient and oncologist completed the questionnaires independently. The pre-treatment questionnaire included an open-ended question on their treatment goals. In the post-treatment questionnaire, the exact goals provided on the first questionnaire were copied on the second questionnaire. For each goal, respondents were asked to what extent it was achieved using a response scale of 0-10 (see appendix, figure A). In addition, the second questionnaire contained the question: In hindsight, do you think it was a right decision to start this treatment? Patients also filled out the validated EORTC-QLQ-C15 quality of life questionnaire.[14] Patient and/or treatment characteristics were retrieved from the questionnaire or medical records.

Data analysis

The goals patients and oncologists described in the open-ended question were coded. From a subset of 145 questionnaires filled out by patients and oncologists, the goals listed were coded independently and subsequently compared by 4 research team members (HRWP, BDO, AM, AB). Discrepancies were resolved through discussion until 100% agreement was achieved. The remaining 116 questionnaires from patients and 115 from oncologists were coded by one researcher (AM) and discussed with the research team. This resulted in goals being categorized into four main groups: 'quality of life', 'decreased tumour size', 'life prolongation' and 'cure'; these groups were used in our analyses.[10] See appendix for all goals and categories (Table A). We dichotomized the scores by the extent to which the goal was achieved (0-10). We used a cut off value of 7 or higher to define goals as achieved, because the qualitative interviews showed that patients and oncologists generally regarded goals as achieved if rated with at least a 7. We conducted a sensitivity analyses by performing the regression analyses with a cut off score of 6 (see appendix table D and E).

Statistical analyses were conducted using IBM SPSS statistics 24. Differences between the demographic characteristics were tested with Analysis of Variance (ANOVA) for the continuous variable of age and with a chi-square test for dichotomous and nominal variables. A Generalized Estimated Equation (GEE) was used to attain understanding of the association between patient and healthcare characteristics and the achievement of treatment goals

(dependent variable). By using the oncologists as a subject variable (23 oncologists provided information on their treatment goals for the included patients), GEE avoids the cluster effect present in the commonly used logistic regression models. The individual level of observation in this analysis is the treatment goal (and not patient or oncologist) in order to analyse the relation between type of treatment goal and achievement of goals. We did not correct for clustering on the patient level as there were too few observations (goals) per cluster. Among patients, 56% of clusters had 1 observation and 39% of clusters had 2 observations. Among oncologists, 26% of clusters had 1 observation and 57% of clusters had 2 observations. The independent variables used in the analyses were age, sex, marital status, educational level, being religious, presence of comorbidity, histology of the tumour, and performance status (ECOG (Eastern Cooperative Oncology Group) score 0, 1, ≥2)), type of systemic treatment for metastatic lung cancer, line of systemic treatment and hospital type. Karnofsky scores were recoded into an ECOG score (90-100% = 0, 70-80%=1, 50-60% =2, 30-40%=3, 10-20%=4).[15] Each statistically significant variable in the univariate GEE analyses ($p<0.10$) was entered into a multivariable GEE model. The final model was derived using the backward selection method, with a P-value of <0.05 considered statistically significant. Results of the GEE regression analyses are presented as odds ratios (ORs) and associated 95% confidence intervals (CIs).

Additional semi-structured qualitative interviews

In order to understand the outcomes of patients and oncologists from the questionnaire study, additional interviews were conducted with 15 patients (17 were invited, 15 agreed to participate) from the academic hospital, and their 5 oncologists. Patients were recruited using purposive sampling to ensure as much variation as possible. Criteria that drove the purposive sampling were whether participants' goals were achieved or not achieved, what type of treatment goals were mentioned, gender and age. Potential participants were contacted by telephone and received an information letter. All participants gave written informed consent prior to the interview. Patients received a gift voucher for their participation.

All in-depth interviews were performed by one researcher (HTK) between November 2018 until March 2019 at the participant's home or the hospital. Participants were asked to explain their answers in the questionnaire using a semi-structured interview guide (see appendix, table B). The length of the interviews ranged from 40-70 minutes for patients and 25-35 minutes for oncologists. All interviews were audio recorded and transcribed verbatim. A summary of the interview of about 400 words was sent to the participant to confirm that some of the answers were interpreted correctly. However, none of the participants disagreed with the interpretations. We followed the principles of thematic analysis.[16] Three transcripts were coded independently by three researchers (HRWP, BDO, HTK) using Atlas.ti 7 and thereafter discussed intensively. Subsequently, all remaining interviews were coded by one researcher (HK). Codes were then discussed with other researchers (HRWP, BDO, AM, AB) and grouped in themes.

Ethics, consent and permission

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, the Netherlands (number NL57455.029.16). Both patients and oncologists gave written consent to participate in the study and for patients to have their medical records reviewed. Transcripts were anonymized after transcription. Access to the data was limited to five researchers.

Results

Sample characteristics

In total, 376 eligible patients with metastatic lung cancer were approached. Of these, 266 patients and 23 oncologists for 260 patients signed informed consent and filled out a questionnaire on their treatment goals before treatment. After systemic treatment, 146 patients and 23 oncologists for 223 patients completed the second questionnaire (61% and 95% respectively) (see figure 1). Patients and oncologists reported 1,5 and 1,9 treatment goals on average respectively [range: 1-4].

Patients who filled out the questionnaire after treatment (n=146) and patients who had not filled out the questionnaire after treatment (because they died during the treatment (n=72) or for other reasons (n=22)), were compared on all characteristics. Differences were found only for ECOG performance status. (See appendix, table C).

Among the 146 patients, 61 patients had received chemotherapy (42%), 65 patients had received immunotherapy (44%) and 20 patients had received TKIs (14%). Demographic characteristics of these patients are presented in table 1.

Achievement of defined goals after a systemic treatment according to patients and oncologists

All 146 patients scored the extent to which their defined treatment goals (219 in total) were achieved. All 23 oncologists did the same for the 428 defined treatment goals they identified for 223 patients. Scores ranged from 0 to 10, with a score of 0 being given relatively frequently especially among oncologists (figure 2). Using a cut-of-score of 7, patients reported the goals ‘quality of life’, ‘life prolongation’, ‘decrease in tumour size’ and ‘cure’ as achieved in 30%, 49%, 26% and 44% respectively. When asked whether their treatment goals had changed over the course of treatment, 72% of patients responded there had been no change in goals. Noted changes were primarily related to lowering expectations due to a worsening condition or realizing expectations were too high.

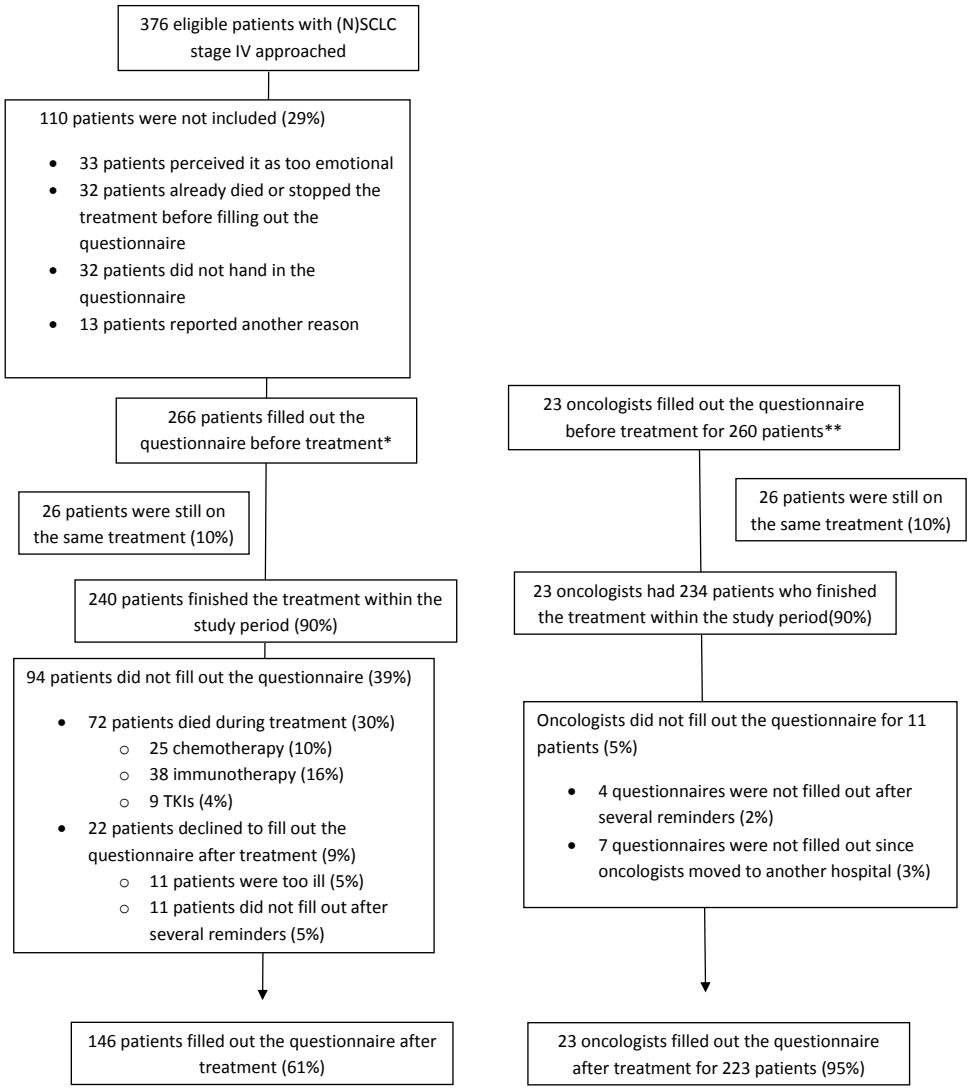

Figure 1. Flowchart recruitment of patients and oncologists. * From the included 266 patients, 19 patients participated twice for different lines of therapy. ** For 6 of the 266 patients the oncologist did not fill out the questionnaire before treatment.

Oncologists reported the goals 'quality of life', 'life prolongation' and 'decrease in tumour size' as achieved in 37%, 41% and 44% respectively. The goal of 'cure' was mentioned three times by oncologists. This number was too small to include in the analysis.

Table 1. Demographic characteristics of study participants

Variable	Chemotherapy	Immunotherapy	TKIs	Total
Patients; N (column %)	N=61 (42%)**	N=65 (44%)	N=20 (14%)	N=146 (100%)
Age – Years (Mean±SD)	63±9	64±8	67±12	64±9
Sex				
Male	37 (61)	39 (60)	7 (35)	83 (57)
Female	24 (39)	26 (40)	13 (65)	63 (43)
Marital status				
Married	49 (80)	49 (75)	16 (80)	114 (78)
Unmarried	12 (20)	16 (25)	4 (20)	32 (22)
Education *				
Low	12 (21)	16 (28)	3 (17)	31 (24)
Middle	30 (54)	24 (42)	9 (50)	63 (48)
High	14 (25)	17 (30)	6 (23)	37 (28)
Religious				
Yes	26 (43)	26 (40)	8 (40)	60 (41)
No	35 (57)	39 (60)	12 (60)	86 (59)
Comorbidity				
Yes	39 (64)	41 (66)	10 (53)	90 (63)
No	22 (36)	21 (34)	9 (47)	52 (37)
ECOG performance score *				
0	14 (27)	15 (25)	0 (0)	29 (22)
1	30 (58)	30 (50)	12 (71)	73 (55)
≥ 2	8 (15)	15 (25)	5 (29)	30 (23)
Tumour histology				
SCLC	8 (13)	0 (0)	0 (0)	8 (6)
NSCLC with targetable driver mutation	13 (21)	8 (12)	19 (95)	40 (27)
NSCLC without targetable driver mutation	40 (66)	57 (88)	1 (5)	98 (67)
Line of treatment				
1st	**38 (62)**	13 (20)	7 (35)	58 (40)
2nd	12 (20)	**43 (66)**	5 (25)	60 (41)
≥ 3rd	11 (18)	9 (14)	**8 (40)**	28 (19)
Treatment duration				
<2 months	31 (51)	25 (39)	6 (30)	62 (43)
2-3 months	20 (33)	4 (6)	0 (0)	24 (16)
3-6 months	6 (10)	14 (22)	2 (10)	22 (15)
6-12 months	3 (5)	5 (8)	5 (25)	13 (9)
12> months	1 (1)	17 (26)	7 (35)	25 (17)
Hospital type				
Academic	29 (47)	**61 (94)**	**17 (85)**	107 (73)
Non-academic	**32 (53)**	4 (6)	3 (15)	39 (27)

Continue

Continued

Variable	Chemotherapy	Immunotherapy	TKIs	Total
Oncologists; N (column %)				N=23 (100%)
Sex oncologist				
Male				8 (35)
Female				15 (65)
Age oncologist				
< 40				10 (43)
41-50				10 (43)
≥ 51				3 (14)
Hospital type				
Academic				11 (48)
Non-academic				12 (52)

TKIs: Tyrosine Kinase Inhibitors; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer.
* Denotes more than 5% missing cases; education: 9%, ECOG performance score: 9%
** 6 patients who received a combined chemotherapy and TKI study treatment were included in the chemotherapy group
Bold values indicate a difference with a p-value of ≤0.05.

There were 72 patients who died during the treatment. The oncologists for these patients completed the questionnaire after treatment. They perceived their treatment goals for these patients to be achieved in 26% for 'quality of life', in 19% for 'life prolongation' and in 35% for 'decrease in tumour size' (data not shown).

Patient and care characteristics associated with achievement of treatment goals

Patients more often perceived their goal as achieved when they had a higher score on quality of life measures. Patients who received TKIs perceived their defined treatment goals as achieved less often than patients who received chemotherapy (table 2).

Both patients and oncologists perceived their treatment goals as achieved more often when the patient received a longer duration of treatment. In addition, for both patients and oncologists, there was no association between achievement of goals and whether the goal was 'quality of life', 'life prolongation', 'decrease in tumour size' or 'cure' (table 2 and 3).

In a sensitivity analyses using a cut-off score of 6 or more as having achieved a goal, there was no difference in the factors associated with goals being achieved compared to the primary analysis that used a cut-off score of 7 or more. Among patients, older age was also positively related to goals being achieved and among oncologists, receiving immunotherapy and having a higher ECOG performance score were negatively related to goals being achieved (See appendix table D and E).

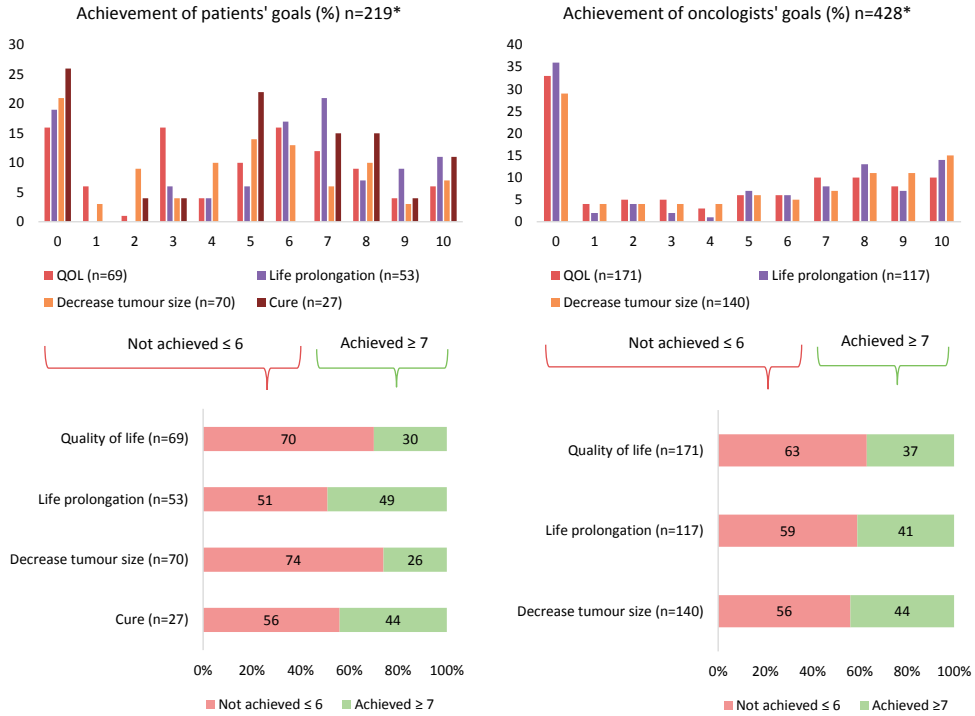

Figure 2. Achievement of treatment goals. * Patients (n=146) had 219 goals together, oncologists had 428 goals together (for n=223 patients)

The right decision to start treatment according to patients and oncologists

Seventy-nine percent (79%) of patients, in hindsight, felt that they had made the right decision to start a systemic treatment. Among patients who had achieved and not achieved their goals, 92% and 72% respectively felt they had made the right decision to start systemic treatment. Oncologists felt they had made the right decision to start a systemic treatment in 96% of cases. Among cases where oncologists had achieved goals vs. not achieved goals, 100% and 93% respectively felt they had made the right decision to start systemic treatment.

Further insight in achievement of treatments goals and starting a treatment was the right decision

Some patients mentioned in the interviews they perceived their goal as achieved if there seemed to be some positive effect on their treatment goal, e.g. slow progression of the tumour instead of the expected fast progression for the goal 'to slow the cancer'. This often affected their health situation positively for a shorter or longer period of time. 'Quality of life' was perceived as achieved because patients' quality of life was reasonable at that moment. (Table 4, Q1) One interviewed patient said that his goal 'cure' was achieved, because he still was alive (Table 4, Q2).

Table 2. Univariate and multivariate GEE analyses of factors associated with achievement of treatment goals according to patients

N=219 Variable (N)	Goal achieved (≥7) according to patient (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Age–Years			
≤60 (76)	32	1.0	
61-70 (100)	36	1.219 (0.647 – 2.295)	
≥71 (43)	40	1.417 (0.650 – 3.089)	
Sex			
Male (126)	37	1.177 (0.761 – 1.820)	
Female (93)	33	1.0	
Marital status			
Married (179)	35	1.062 (0.595 – 1.897)	
Unmarried (40)	35	1.0	
Education			
Low (47)	28	1.0	
Middle (95)	35	1.387 (0.530 – 3.627)	
High (60)	37	1.627 (0.571 – 4.630)	
Religious			
Yes (88)	36	1.041 (0.388 – 2.792)	
No (131)	35	1.0	
Comorbidity			
Yes (135)	37	1.062 (0.493 – 2.288)	
No (76)	36	1.0	
ECOG performance score			
0 (39)	49	1.0	
1 (111)	31	0.520 (0.222 – 1.213)	
≥ 2 (46)	30	0.478 (0.177 – 1.285)	
Quality of life (mean ± stdev)	4.6 ± 1.6	**1.716 (1.408 – 2.092)**	**1.545 (1.299 – 1.837)**
Tumour histology			
SCLC (13)	39	1.0	
NSCLC without targetable driver mutation (152)	39	1.030 (0.156 – 6.790)	
NSCLC with targetable driver mutation (54)	24	0.486 (0.086 – 2.752)	
Type of systemic treatment			
Chemotherapy (92)	42	1.0	1.0
Immunotherapy (100)	33	0.637 (0.280 – 1.453)	0.381 (0.133 – 1.090)
TKIs (27)	19	**0.280 (0.090 – 0.872)**	**0.157 (0.049 – 0.503)**
Line of treatment			
1st (84)	44	1.0	
2nd (96)	31	**0.512 (0.351 – 0.747)**	
≥ 3rd (39)	26	0.432 (0.144 – 1.295)	
Treatment duration			
<2 months (95)	21	1.0	**1.0**
2-6 months (64)	42	**2.612 (1.187 – 5.750)**	1.615 (0.784 – 3.327)
> 6 months (60)	50	**3.432 (1.075 – 10.957)**	**3.686 (1.016 – 13.375)**
Hospital type			
Academic (164)	35	1.007 (0.557 – 1.822)	
Non-academic (55)	35	1.0	
Treatment goal			
Quality of life (69)	30	1.0	
Decrease in tumour size (70)	26	0.871 (0.293 – 2.594)	
Cure (27)	44	**1.910 (0.927 – 3.937)**	
Life prolongation (53)	49	**2.263 (1.120 – 4.573)**	

OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.10 for the univariate model and with a p-value of ≤0.05 for the multivariate model.

Table 3. Univariate and multivariate GEE analyses of factors associated with achievement of treatment goals according to oncologists

N=428 Variable (N)	Goal achieved (≥7) according to oncologists (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Age–Years			
≤60 (120)	52	1.0	
61-70 (182)	30	**0.422 (0.201 – 0.886)**	
≥71 (124)	48	0.782 (0.518 – 1.180)	
Sex			
Male (226)	40	1.0	
Female (202)	43	1.056 (0.601 – 1.855)	
Marital status			
Married (337)	39	1.0	
Unmarried (90)	50	**1.445 (0.883 – 2.365)**	
Education			
Low (79)	51	1.0	
Middle (186)	36	0.606 (0.322 – 1.139)	
High (107)	49	1.053 (0.361 – 3.075)	
Religious			
Yes (167)	41	1.0	
No (261)	42	1.067 (0.652 – 1.746)	
Comorbidity			
Yes (272)	38	1.0	
No (142)	47	1.637 (0.753 – 3.560)	
ECOG performance score			
0 (60)	55	1.0	
1 (194)	45	0.661 (0.373 – 1.170)	
≥ 2 (105)	31	**0.343 (0.140 – 0.838)**	
Quality of life (mean ± stdev)	4.6 ± 1.6	**1.355 (1.112 – 1.653)**	
Tumour histology			
SCLC (25)	36	1.0	
NSCLC without targetable driver mutation (296)	37	1.211 (0.745 – 1.970)	
NSCLC with targetable driver mutation (107)	55	**2.456 (1.121 – 5.378)**	
Type of systemic treatment			
Chemotherapy (175)	39	1.0	
Immunotherapy (192)	35	0.763 (0.266 – 2.184)	
TKIs (61)	69	**3.191 (1.851 – 5.501)**	
Line of treatment			
1st (196)	41	1.0	
2nd (174)	38	0.864 (0.479 – 1.558)	
≥ 3rd (58)	53	1.451 (0.706 – 2.984)	
Treatment duration			
<2 months (183)	12	1.0	1.0
2-6 months (133)	45	**5.905 (2.437 – 14.312)**	**5.905 (2.437 – 14.312)**
> 6 months (106)	86	**47.651 (13.742 – 165.229)**	**47.651 (13.742 – 165.229)**
Patients who died during treatment			
Yes (114)	30	1.0	
No (314)	46	**2.105 (1.285 – 3.450)**	

Continue

Continued

N=428 Variable (N)	Goal achieved (≥7) according to oncologists (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Hospital type			
Academic (309)	43	1.367 (0.619 – 3.022)	
Non-academic (119)	37	1.0	
Treatment goal			
Quality of life (171)	39	1.0	
Decrease in tumour size (140)	44	1.089 (0.806 –1.471)	
Life prolongation (117)	43	1.147 (0.890 – 1.476)	

OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.10 for the univariate model and with a p-value of ≤0.05 for the multivariate model.

Other patients mentioned that they perceived their goal as not achieved when the treatment had a negative effect and when their health situation had deteriorated. For example, the goal 'cure' had not been achieved because the treatment had not affected the size of the tumour, or the goal 'best possible quality of life' had not been achieved because the patient permanently lost all energy due to the treatment.

Although some patients stated that they were deeply disappointed when treatment goals had not been achieved, they thought, in hindsight, it was the right decision to start. They had at least tried to achieve their goal in every way possible, because they actively did something to slow the progression of disease, and because 'doing nothing' was not a reasonable option. (Table 4, Q 3-4).

Similar to patients, oncologists perceived their goals as achieved if there was any positive effect on the patients' well-being, whether this was a small or large effect (Table 4, Q5). Treatment goals were perceived as not achieved when the situation of a patient quickly deteriorated, which could also be due to a side effect of the treatment (Table 4, Q6).

Oncologists were disappointed when treatment goals were not achieved, but explained why they often perceived their decision as right in hindsight. First, they mentioned that any one specific patient could have been the one who turned out to be an exception– most often in terms of life extension and therefore, it was the right decision to start treatment (Table 4, Q7). Also, at the start of treatment it seemed to be the right decision at that time. Additional reasons noted by oncologists for perceiving starting a treatment as 'the right decision' in hindsight were that guidelines or the patients' wish had been followed (Table 4, Q8 and Q9).

Table 4. Quotes of patients and oncologists on achievement of goals and why it was the right decision to start treatment

No	*Quotes of patients*
Q1	I: Let me proceed to the questionnaire after treatment, we discuss your treatment goals here: a bit longer, better life with some quality. And then we ask you: to what extent is this achieved, rate it with a number? And your answer is, an 8, because, preserved quality. P: Yes, that is the same as I just mentioned. I feel that right now I, have a reasonable quality of life. With some restriction off course. But I consider myself blessed that I am still clear headed, that I can experience everything, watch TV and Netflix, you name it. I read a book… (Patient with goal 'quality of life' achieved)
Q2	I: And if the question is if your goal is achieved, the goal "cure". What do you mean with the number 8, did you achieve the goal than or not… P: I achieved the goal a little bit. I am still alive, yes, good. But what if the immunotherapy works, than I still have some time to live. There is still hope. The current status, how it is right now. Yes. (Patient with goal 'cure' achieved)
Q3	"You cannot say in advance, I only have 9 months and I throw in the towel. That is nothing for me. (…) And if I do something, than at least I do something. (…) It will bring something, for me or for the doctors or both. That's how I think about it. (Patient with goal 'stop cancer' not achieved)
Q4	I: Let's see the questionnaire, here is the question: in hindsight, do you think that this was de right treatment. You say: if you don't do it, you know for sure that it doesn't work. P: Yes, not trying is no option. And also the hope right. (Patient with goal 'cure' not achieved)
No	*Quotes of oncologists*
Q5	I: Then the questionnaire after the treatment. That one show something else. You rate the goal decrease tumour growth as achieved with the number 9. P: Yes, it worked. I: Yes, did that work? P: Yes, a 9 is achieved. I: And then you say in your questionnaire: I feel that this was the right decision because at first I have seen a response. That 9, can you tell me how that went and what that 9 means? P: That 9 means just, we have tried to decrease the tumour, and that worked. That tumour has become smaller. And that means, look, if you can decrease the growth of the tumour, it means that the tumour delays. That it will grow thereafter, so to say. But you have bought some time then. That is what it is all about.
Q6	I: In the questionnaire after the treatment you report at 'goal achieved' a 0 for the goal stop and decrease the tumour . P: Yes, this man also got Hepatitis. Therewith he deteriorated enormously. I made him worse instead of better [looks sad]"
Q7	P: If that [deterioration] is out of question and the patient feels himself well and you still have a treatment to come and he looks fit…. (…) There is also reality. Seriously, I have patient who live for 10 years with stage 4. I: You have examples, that it works. P: Yes, indeed. So it is not that everyone lives for 1,5 year and then dies. That is not the case.

Continue

Continued

Q8	P: You know in advance that the chance that this treatment succeeds for all goals you mention here, is 20 percent. But that is the best chance you have. According to the guidelines that is your right decision. But you also know in advance that it won't work for 80 percent of the patients. And this patient sadly belong to the 80 percent of people for who it doesn't help. So in hindsight it didn't go wrong. Only what you had hoped or predicted, didn't come through.
Q9	I: And then I see, we ask in the questionnaire, is the right decision made in hindsight to start this treatment, then you say yes because there were no other options… P: Yes, another option would have been not starting treatment [laughs] I: Yes that was wat I wondered by seeing these questions. P: Yes but sometime someone really doesn't want that. And she didn't received any treatment yet I think, no systemic treatment, most of the time people want to try something, at least the people that we see. So in that aspect it was the right treatment for her, yes in hindsight it didn't worked for her. So the specific treatment was in itself a good choice. Only you could have also argued, the condition is too bad we don't do it.

Discussion

The treatment goals that patients defined when starting the treatment 'quality of life', 'life prolongation', 'decrease in tumor size' and 'cure' were perceived as achieved in 30%, 49%, 26% and 44% respectively. For oncologists treatment goals were perceived to be achieved in 37%, 41% and 44% of cases, respectively. Patients with a higher score on quality of life measure and patients who received treatment for more than six months more often perceived their treatment goals as achieved than other patients. Patients who received TKIs were less likely to feel they achieved their treatment goals. Oncologists more often perceived their treatment goals as achieved for patients receiving treatment for two months or more. We found no association between achievement of goals and whether the goal was 'quality of life', 'life prolongation', 'decrease in tumour size' or 'cure'. Most patients and oncologists, in hindsight, felt they had made the right decision to start treatment whether or not they had not achieved their goals. An important reason for this was that they at least had tried something.

Most treatment goals are not achieved

It is noticeable that the majority of treatment goals were not achieved from the perspective of both the patients and oncologists. In prior work we found that both patients and oncologists when starting a treatment sometimes doubted feasibility of achieving their treatment goals even when they gave a relatively high score on feasibility. It appeared that hope was more important in considering a treatment feasible than actual chances on success.[10, 17] In the current study, the goal 'decrease in tumour size' was much less often reported as achieved

by patients (26%) compared to oncologists (44%). It could be that oncologists report this goal as achieved with even small decreases in the size of the tumour, while patients only consider substantial decrease as achieving this goal. Only 1 out of 3 patients and oncologists perceived 'quality of life' as achieved. This is of concern, as quality of life is often mentioned as important aspect in the last phase of life. Interestingly, among the 27 patients who identified 'cure' as a treatment goal, 44% (12 patients) reported this goal as achieved. This goal is unrealistic as metastatic lung cancer cannot be cured and might be a form of hope. This is supported by patient statements in our qualitative interviews (see table 4, Q2).

It seems logical that patients with higher quality of life perceive their goals more often as achieved as they probably feel better. However, it is less straightforward why this is the case for the other goals. A possible explanation for the fact that patients who received TKIs less often achieved their treatment goals might be related to the fact that TKI's are often seen as a promising treatment[18]; higher expectations might lead to more disappointment and lower achievements scores. The finding that for both patients and oncologists treatment goals are more often achieved when the treatment duration is longer, is likely to be related to treatment being stopped when the condition of the patient worsens.

Patients and oncologists feel starting the treatment was the right decision

Four out of five patients (79%) and oncologists (96% of cases) felt, in hindsight, that they had made the right decision to start treatment. The qualitative interviews showed that wanting to do 'something' was an important factor for both patients and oncologists in feeling that starting treatment was the right decision. This importance of doing 'something' resonates with other studies.[19, 20] There are few previous studies that evaluate satisfaction with treatment decisions among advanced cancer patients.[21] Visser et al. found that 86% of patients with advanced lung cancer indicated that they would decide to undergo the same treatment again, regardless of deterioration or improvement in quality of life.[21] Umihara et al. found that among patients who had received cancer treatment, 67% of patients were satisfied with their decision, and that satisfaction was related to good patient physician communication.[22] Hitz et al. found among patients with advanced cancer 73% satisfaction with treatment decision.[23]

Strengths and limitations

Strengths of our study include the contribution of both academic and non-academic hospitals, use of open-ended questions for respondents to formulate goals in their own words and the additional interviews to better understand respondents answers. A limitation of our study is that we only interviewed patients and oncologists from the academic hospital, possibly giving bias to the additional information.

Conclusion and implications

Our finding that most patients and oncologists, in hindsight, feel starting treatment was the right decision while indicating that most treatment goals were not achieved is not easy to interpret. One could interpret this as a good outcome because patients and oncologists feel they made the right decision. However, even when not considering the cost of treatment, one can question whether starting treatments that are likely not to achieve stated goals are in the best interest of patients. The interviews indicate that wanting to do 'something' was important for both patients and oncologists in their assessment that starting treatment was the right decision. This suggests that if there were other options to do something that had a higher possibility of reaching goals, this might be preferable. When the goal is quality of life, which was achieved only in 1 in 3 patients, palliative care could be such an option. In addition, when the goal is life prolongation, (concurrent) palliative care is a good option as several studies have shown that early initiation of palliative care can prolong life.[24, 25] In order for these approaches to work in practice it is important that treatment options, including their benefits and side-effects, are discussed in advance of treatment decisions. It is key that these discussions include not only systemic treatment, but palliative care as effective options for doing 'something'. Our results could provide valuable input for these discussions.

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APPENDIX

Questionnaire for patients:

- "*Before the treatment, you mentioned the following treatment goals. To what extent are these goals achieved on a scale of 0 to 10*?"

1._[Goal 1 is written here]_____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

2._[Goal 2 is written here _____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

3._[Goal 3 is written here]_____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

4._[Goal 4 is written here]_____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

- "*In retrospect, did you receive enough information on the treatment*?"
Too much/ enough/ not enough
This is what I missed: _____

- "*In hindsight, do you think the right decision was made for treatment*?"

  Yes/ No / I don't know for sure

- *Did the treatment goals you had before the start of treatment, change during treatment?*
  - Yes, namely
  - No

Questionnaire for oncologists:

- "*Before your patient started the treatment, you mentioned the following treatment goals. To what extent are these goals achieved on a scale of 0 to 10*?"

1._[Goal 1 is written here]_____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

2._[Goal 2 is written here _____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

3._[Goal 3 is written here]_____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

4._[Goal 4 is written here]_____
0 1 2 3 4 5 6 7 8 9 10
not achieved at all highly achieved

- "*In hindsight, do you think the right decision was made for treatment*??"

Yes/ No / I don't know for sure

Figure A. Questionnaires for patients and oncologists

Table A. Examples of treatment goals from patients and oncologists

Category	**English**
Quality of life	Having a more comfortable life
	Better quality of life
	Better mobility
	Feeling better
	Being able to do more things than I can do now
	The best quality of life
	Making the quality of life as high as possible
	Having a bearable life
	Having a pleasant life
	Good quality of life
	Quality of life
	Improve quality of life
	Improve life
	Strive for a better life than I have now
	Living life to the fullest
	Pain relieve
	Improvement
	Improve life circumstances
	Relieve dyspnoea
	Less symptoms
	More oxygen
	Less pleural effusion
	Being less ill
Decrease in tumour size	Decrease tumour carcinoma
	Slow down tumour
	Slow down metastases
	Restriction of tumours
	To stop cancer cells from growing
	To stop the cancer
	To prevent the cancer from growing
	To control cancer
	That the cancer disappears
	To decrease the tumour cells
	That the tumour disappears
	That it does not grow any further
	High stabilization of the disease
	To fight the cancer
	Prevent new metastases
	To stop the tumour from growing
	To delay the cancer process
	To stop the cancer
	Stopping the disease process
	To shrink the tumour
	To slow down the disease
	To slow down the cells

Continue

Continued

Category	**English**
	Staying stable
	Stop the cancer
	To withhold the tumour
	To shrink the tumour
	To delay the growth
Life prolongation	Better life opportunities
	To live longer
	To enjoy time with my partner as long as possible
	A future
	Extra time
	To live longer
	Longer lifespan
	To prolong life
	Life prolongation
	More time
	To live as long as possible
	Time gain
	Postpone death
	To prolong life
Cure	Getting better
	That I recover
	Cured
	Recovery
	Regain one's health
	Prefer speedy recovery
	Gain health
Other	Visiting Suriname
	Nothing
	To keep the option for radiation
	To quit
	To do everything about it
	Improve medication for future patients
	To contribute to science
	So that specialists can learn
	To have the feeling I have tried everything
	Gain more insight in research
	To keep the option for immunotherapy

Table B. Interview guides for semi-structured interviews with patients and oncologists

Interview guide for semi-structured interviews with patients	Interview guide for semi-structured interviews with oncologists

• Introducing the subjects, aim of the interview
• Bringing up previously completed questionnaires before and after treatment
• Informed consent and audio recording
• Introductory question: asking the participant how he/she lately experienced health and illness
• Preparation of treatment choice and treatment goals
  ◦ Important values for the patient
  ◦ Reason for setting mentioned goals (e.g. cure)
  ◦ Discussing goals with the oncologist
  ◦ No treatment as an option
• Achieved goals
  ◦ Explanation of score at goal achieved / not achieved
  ◦ Explanation of satisfaction when goals are (not) achieved
  ◦ Explanation of score at quality of life
• Evaluation afterwards
  ◦ Do the same / differently afterwards (e.g. preparation)
  ◦ Advices for oncologists
• Verbal summary and member check
• Gift voucher
	• Introducing the subjects, aim of the interview
	• Bringing up previously completed questionnaires before and after treatment
	• Informed consent and audio recording
	• Introductory question: asking the participant how he/she remembers the patients
	• Reasons for setting mentioned goals (e.g. survival)
	  ◦ Underlying explanation of mentioning these goals in
	  ◦ terms of achievement
	  ◦ Used terms regarding
	  ◦ Discussing goals with the oncologist
	  ◦ No treatment as an option
	• Achieved goals
	  ◦ Explanation of score at goal achieved / not achieved
	  ◦ Explanation of satisfaction when goals are (not) achieved
	  ◦ Explanation of score at quality of life
	• Evaluation afterwards
	  ◦ Do the same / differently afterwards (e.g. preparation)
	  ◦ Advices for oncologists
	• Verbal summary and member check
	• Gift voucher

Table C. Comparison of patients who filled out questionnaire or not

	Filled out questionnaire	Did not fill out questionnaire		
N=240 Variable (N) (column %)	**Patients who filled out N=146**	**Patients who died N=72**	**Patients who declined N=22**	**P-value**
Age – Years				
<60 (71)	33	26	14	
61-70 (102)	42	42	50	
≥ 71 (67)	25	32	36	0.311
Sex				
Male (131)	57	54	41	
Female (109)	43	46	59	0.374
Marital status				
Married (186)	78	79	68	
Unmarried (54)	22	21	32	0.538
Comorbidity				
Yes (154)	63	67	81	
No (79)	37	33	19	0.227
ECOG performance score				
0 (35)	22	3	21	
1 (111)	55	51	53	
≥ 2 (60)	23	**46**	26	**0.005**
Tumour histology				
SCLC (13)	6	4	9	
NSCLC without targetable driver mutation (170)	67	75	82	
NSCLC with targetable driver mutation (57)	27	21	9	0.324
Type of systemic treatment				
Chemotherapy (94)	42	35	36	
Immunotherapy (116)	44	53	59	
TKIs (30)	14	12	5	0.524
Line of treatment				
1st (99)	40	43	46	
2nd (103)	41	46	46	
≥ 3rd (38)	19	11	8	0.525
Hospital type				
Academic (177)	73	69	91	
Non-academic (63)	27	31	9	0.132

ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.05.

Table D. Univariate and multivariate GEE analyses of factors associated with achievement of treatment goals according to patients

N=219 Variable (N)	Goal achieved (≥6) according to patient (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Age–Years			
≤60 (76)	40	1.0	1.0
61-70 (100)	53	1.661 (0.908 – 3.041)	**4.938 (2.249 – 10.846)**
≥71 (43)	56	**1.937 (0.908 – 4.131)**	**3.098 (1.174 – 8.178)**
Sex			
Male (126)	49	1.097 (0.675 – 1.785)	
Female (93)	47	1.0	
Marital status			
Married (179)	48	0.920 (0.512 – 1.652)	
Unmarried (40)	50	1.0	
Education			
Low (47)	51	1.0	
Middle (95)	46	0.775 (0.361 – 1.662)	
High (60)	47	0.904 (0.309 – 2.639)	
Religious			
Yes (88)	44	1.0	
No (131)	51	1.365 (0.473 – 3.942)	
Comorbidity			
Yes (135)	52	1.341 (0.646 – 2.781)	
No (76)	46	1.0	
ECOG performance score			
0 (39)	54	1.0	
1 (111)	47	0.848 (0.323 – 2.225)	
≥ 2 (46)	46	0.755 (0.291 – 1.959)	
Quality of life (mean ± stdev)	4.6 ± 1.6	**1.927 (1.482 – 2.507)**	**2.001 (1.501 – 2.667)**
Tumour histology			
SCLC (13)	46	1.0	
NSCLC without targetable driver mutation (152)	50	1.247 (0.168 – 9.248)	
NSCLC with targetable driver mutation (54)	44	1.056 (0.151 – 7.375)	
Type of systemic treatment			
Chemotherapy (92)	53	1.0	1.0
Immunotherapy (100)	47	0.684 (0.289 – 1.617)	0.489 (0.165 – 1.446)
TKIs (27)	37	**0.516 (0.262 – 1.018)**	**0.277 (0.091 – 0.847)**
Line of treatment			
1st (84)	55	1.0	
2nd (96)	45	**0.615 (0.355 – 1.067)**	
≥ 3rd (39)	55	0.642 (0.238 – 1.731)	
Treatment duration			
<2 months (95)	31	1.0	1.0
2-6 months (64)	55	**2.617 (1.323 – 5.179)**	2.176 (0.990 – 4.785)
> 6 months (60)	70	**4.966 (1.871 – 13.185)**	**6.449 (2.632 – 15.802)**
Hospital type			
Academic (164)	49	1.169 (0.526 – 2.595)	
Non-academic (55)	46	1.0	
Treatment goal			
Quality of life (69)	46	1.0	
Decrease in tumour size (70)	39	0.792 (0.321 – 1.955)	
Cure (27)	44	0.950 (0.424 – 2.133)	
Life prolongation (53)	66	**2.233 (1.134 – 4.337)**	

OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.10 for the univariate model and with a p-value of ≤0.05 for the multivariate model.

Table E. Univariate and multivariate GEE analyses of factors associated with achievement of treatment goals according to oncologists

N=428 Variable (N)	Goal achieved (≥6) according to oncologists (row %)	Univariate OR (95%-CI)	Multivariate OR (95%-CI)
Age–Years			
≤60 (120)	55	1.0	
61-70 (182)	37	**0.489 (0.266 – 0.900)**	
≥71 (124)	53	0.846 (0.576 – 1.242)	
Sex			
Male (226)	46	1.0	
Female (202)	49	1.068 (0.632 – 1.806)	
Marital status			
Married (337)	45	1.0	
Unmarried (90)	53	1.323 (0.843 – 2.077)	
Education			
Low (79)	57	1.0	
Middle (186)	42	**0.685 (0.444 – 1.056)**	
High (107)	53	1.133 (0.443 – 2.894)	
Religious			
Yes (167)	46	1.0	
No (261)	48	1.088 (0.652 – 1.815)	
Comorbidity			
Yes (272)	44	1.0	
No (142)	49	1.359 (0.609 – 3.030)	
ECOG performance score			
0 (60)	62	1.0	1.0
1 (194)	49	**0.573 (0.348 – 0.942)**	**0.468 (0.217 – 1.009)**
≥ 2 (105)	34	**0.310 (0.142 – 0.678)**	**0.338 (0.114 – 1.000)**
Quality of life (mean ± stdev)	4.6 ± 1.6	**1.518 (1.286 – 1.792)**	
Tumour histology			
SCLC (25)	56	1.0	
NSCLC without targetable driver mutation (296)	42	0.673 (0.241 – 1.880)	
NSCLC with targetable driver mutation (107)	60	1.358 (0.376 – 4.902)	
Type of systemic treatment			
Chemotherapy (175)	46	1.0	1.0
Immunotherapy (192)	40	0.711 (0.287 – 1.761)	**0.356 (0.153 – 0.829)**
TKIs (61)	72	**2.869 (1.461 – 5.634)**	0.651 (0.171 – 2.478)
Line of treatment			
1st (196)	49	1.0	
2nd (174)	43	0.783 (0.437 – 1.401)	
≥ 3rd (58)	53	1.046 (0.534 – 2.047)	
Treatment duration			
<2 months (183)	14	1.0	1.0
2-6 months (133)	55	**6.817 (3.747 – 12.403)**	**7.356 (3.298 – 16.407)**
> 6 months (106)	92	**72.613 (19.245 – 273.970)**	**134.476 (25.721 – 703.069)**
Patients who died during treatment			
Yes (114)	34	1.0	
No (314)	52	**2.114 (1.207 – 3.702)**	
Hospital type			
Academic (309)	47	1.006 (0.452 – 2.237)	
Non-academic (119)	47	1.0	
Treatment goal			
Quality of life (171)	45	1.0	
Decrease in tumour size (140)	49	1.111 (0.834 –1.480)	
Life prolongation (117)	47	1.065 (0.868 – 1.307)	

OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors. Bold values indicate a difference with a p-value of ≤0.10 for the univariate model and with a p-value of ≤0.05 for the multivariate model.

6

RELATIVES OF DECEASED PATIENTS WITH METASTATIC LUNG CANCER'S VIEWS ON THE ACHIEVEMENT OF TREATMENT GOALS AND THE CHOICE TO START TREATMENT: A STRUCTURED TELEPHONE INTERVIEW STUDY

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Abstract

Objective: Lung cancer has a high impact on both patients and relatives due to the high disease burden and short life expectancy. Previous studies looked into treatment goals patients have before starting a systemic treatment. However, studies on relatives' perceptions of treatment at the end of life are scarce.

Aim: Therefore, we studied the perspectives of relatives in hindsight on the achievement of treatment goals and the choice to start treatment for metastatic lung cancer of their loved one.

Methods: We conducted a structured telephone interview study in six hospitals across the Netherlands, one academic and five non-academic hospitals, between February 2017 and November 2019. We included 118 relatives of deceased patients diagnosed with metastatic lung cancer who started a systemic treatment as part of usual care (chemotherapy, immunotherapy or targeted therapy with tyrosine kinase inhibitors (TKIs)) and who completed a questionnaire on their treatment goals before the start of treatment and when treatment was finished. We asked the relatives about the achievement of patients' treatment goals and relatives' satisfaction with the choice to start treatment. This study is part of a larger study in which 266 patients with metastatic lung cancer participated who started a systemic treatment and reported their treatment goals before start of the treatment and the achievement of these goals after the treatment.

Results: Relatives reported the goals 'quality of life', 'decrease tumour size' and 'life prolongation' as achieved in 21%, 37% and 41% respectively. The majority of the relatives (78%) were satisfied with the choice to start a treatment and even when none of the goals were achieved, 70% of the relatives were satisfied. About 50% of relatives who were satisfied with the patients' choice mentioned negative aspects of the treatment choice, such as the treatment did not work, there were side effects or it would not have been the relatives' choice. Whereas, 80% of relatives who were not satisfied mentioned negative aspects of the treatment choice. The most mentioned positive aspects were that they tried everything and that it was the patient's choice.

Conclusion: The majority of relatives reported patients' treatment goals as not achieved. However, relatives were predominantly satisfied about the treatment choice. Satisfaction does not provide a full picture of the experience with the treatment decision considering that the majority of relatives mentioned (also) negative aspects of this decision. At the time of making the treatment decision it is important to manage expectations about the chance of success and the possible side effects of the treatment.

Introduction

Lung cancer is the world's leading cause of cancer death.[1] For patients with metastatic lung cancer chemotherapy, immunotherapy and targeted therapy with tyrosine kinase inhibitors (TKIs) are possible palliative systemic treatments with the aim of relieving symptoms, temporary disease control and prolonging survival.[2-5]

People at the end of life often have diverse physical, psychological and social needs, as well as a need to prepare for death and achieve peace at the end of life.[6-8] While patients and relatives attach great value to fulfilling these needs[8], at the same time there is often hope for a cure or life prolongation.[9, 10]

Three studies found the following treatment goals that patients mentioned before starting treatment for metastatic lung cancer: 'improve or maintain quality of life', 'prolong life', 'find comfort', 'fight cancer' and 'cure cancer'.[11-13] In a previous study we found that after treatment patients reported in less than 50% of time that these goals were achieved: 'quality of life' for 30%, 'life prolongation' for 49%, 'decrease tumour size' for 26% and 'cure' for 44%. Directly after the treatment was finished most patients felt, in hindsight, that starting treatment was the right decision, even if the treatment goals were not achieved.[10]

Metastatic lung cancer has a large impact on both patients and relatives.[14, 15] Relatives often accompany patients to a physician visit and help the patients obtain information relevant to medical treatments.[16-18] Relatives might have an alternative opinion to the patient regarding the choice to start treatment and whether the goals were actually achieved. The relatives witness the patient with metastasized lung cancer from diagnosis to death, and they are able to take into account the last phase of life when considering whether treatment goals are achieved and if the right choice was made. Additionally, the relative has a different perspective since they are not the patient.

Since metastatic lung cancer also affects the life of patient's relatives and not much is known on their views in hindsight the objectives were to study the perspective of relatives on the choice to start lung cancer treatment, after the patient had deceased. We specifically focussed on (1) relatives' perspective regarding achievement of patients' treatment goals, (2) relatives' view on the patients' choice to start treatment and (3) the relation between the achievement of treatment goals and satisfaction with the patient's choice to start treatment.

Methods

Study design and population

The present study is an explorative sub-study of a larger prospective study on achievement of the goals metastatic lung cancer patients and their oncologists have when starting a palliative systemic treatment as part of usual care (chemotherapy, immunotherapy or targeted therapy with tyrosine kinase inhibitors (TKIs)).[10] During the patients' informed consent procedure in

the previous study, patients and relatives were asked to choose a relative to participate in the present study if the patient is deceased. Inclusion criteria were ability to give informed consent, possessing a telephone and willing to participate. During the structured telephone interview with relatives of deceased metastatic lung cancer patients we asked to what extent they felt that the goals patients had when starting a systemic treatment were achieved. The telephone interview was conducted with relatives a minimum of 6 weeks after the patient had died, which we feel is an appropriate time frame to be able to recall the treatment, but it not too early after a loved one has passed. To enhance the rigor in the study, the researcher who interviewed the relatives was transparent, i.e. not the treating physician of the patient. Additionally, the interviews were all conducted in the same way, following the same order in the questionnaire and performed by one researcher (AM, between February 2017 and November 2019).

Data collection

The structured telephone interview schedule was developed based on the questionnaire for patients and oncologists (see appendix 1). During the structured telephone interviews, questions were read aloud and answers were written down textually. The interviews were not audio recorded. The interviews focused on the treatment goal(s) the patient reported before the start of treatment. During the interview relatives were asked to what extent they perceived the patients' treatment goal(s) as achieved on a scale from 0 to 10, with 0 as not achieved at all and 10 as completely achieved. Additionally, relatives were asked if they were satisfied with the patients' choice to starting treatment and whether the relatives thought they received enough information on the given treatment of the patient (see appendix). The relatives' age, gender and relation to the patient were documented.

The time between the patient's death and the interview with their relative was on average 86 days, with the exception of one relative that was interviewed 15 days after the patient died, instead of 6 weeks after the patient died, because the investigator did not know the patient had already died when she called for the study among patients. The relative preferred to do the interview at that time rather than later. The time between the last administration of treatment the patient received and the interview with the relative was on average 201 days.

Ethics, consent and permission.

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, the Netherlands (number NL57455.029.16). Both patients and relatives gave written consent to participate in the study and for patients to have their medical records reviewed. Relatives were able to withdraw their consent at any time.

Data analysis

Descriptive statistics were conducted using IBM SPSS statistics 24. We perceived a goal as achieved if it was rated with a 7 or higher (on a 0 to 10 scale). This was based on the semi-structured interviews performed in the previous study in which we asked the patients to what extent they felt their treatment goals were achieved on a scale from 0 to 10.[19] The question on the satisfaction with the treatment choice in hindsight was to be answered with 'yes', 'no' or 'I am not sure' and additionally open-ended for further explanation. The answers 'no' and 'I am not sure' were for analysis merged into 'not satisfied'. Answers to this open-ended question were categorized independently and subsequently compared by 4 research members (HRWP, BDO, AM, AB). The codes agreed upon were grouped in the categories 'positive aspects', 'negative aspects' and 'other aspects'. Discrepancies were resolved through discussion until 100% agreement was achieved.

Results

Participant recruitment

In total, 266 patients started a treatment for metastatic lung cancer and completed the questionnaire on their treatment goals. Of these patients, 164 patients were deceased during the study period, resulting in 164 relatives being eligible for participation of which 118 (72%) participated in an interview (figure 1). Refusing of participation during the informed consent procedure was in most of the cases because the patient didn't want to bother their relatives with the study in which he or she participated. Decline in participation during the telephonic interview was because the relative already died, telephonic number was not in use or the phone was not picked up after trying several times on different days and times.

Characteristics of study participants

Participants had an average age of 62 years and ranged between 30 and 85 years. Most participants were female (63%) and the partner of the patient (81%) (table 1). Length of the interview was not recorded but roughly lasted between 5 and 60 minutes with an average time of 15 minutes.

Achievement of patients' treatment goals according to relatives

The 118 relatives of patients reported about the achievement of 143 treatment goals with an average of 1.2 goals per patient and a maximum of three goals. In total, 21 patients mentioned 'cure' as a treatment goal. Since only the relatives of deceased patients were included, we did not ask if the goal 'cure' was achieved so we excluded this treatment goal from the analysis. Relatives overall most often reported the achievement of the treatment goal with 0 (not achieved at all) (n=47). Relatives reported the goals 'quality of life', 'life prolongation' and 'decrease in tumour size' as achieved in 21%, 41% and 37% respectively (figure 2).

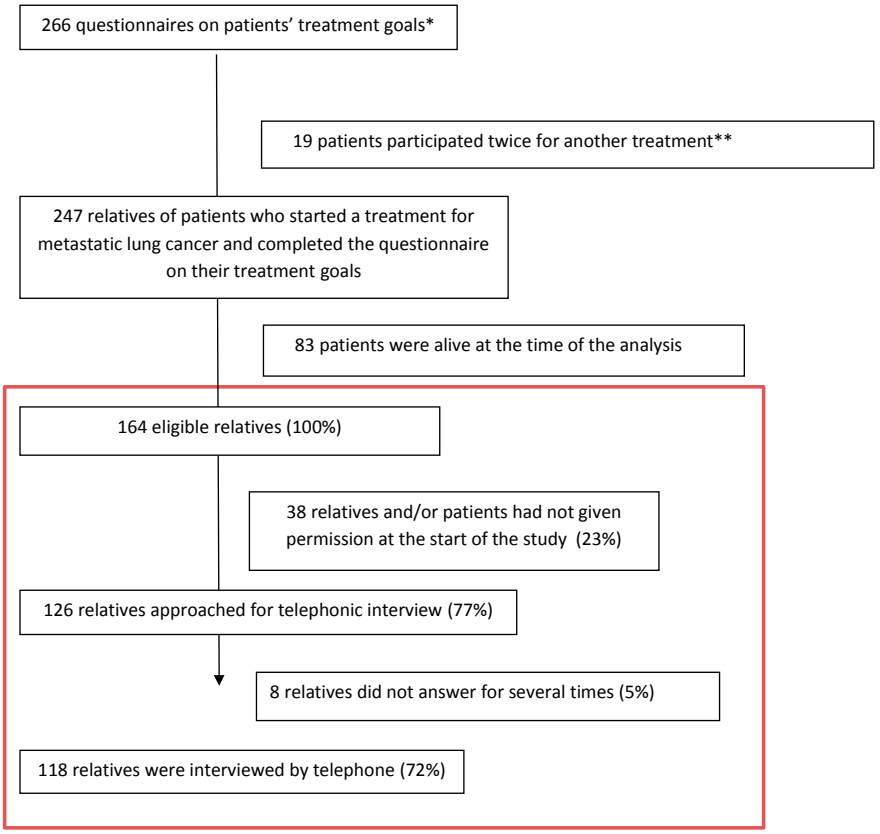

Figure 1. Flowchart of participants. The red box concerns the participants in the current study which is part of a larger study in which 266 patients with metastatic lung cancer participated. In that study, patients could participate multiple times in the study resulting in 247 individual patients from whom the relatives could be approached. Only relatives of deceased patients were eligible to participate. In the end, 118 relatives participated in this interview study. * Consent from patient and relative was asked at the start of the treatment. ** Patients were allowed to participate twice in the questionnaire study when they sequentially received another treatment.

Table 1. Demographic characteristics of study participants (n=118)

Variable	N	%
Age – Years		
Mean ± SD	62 ± 11	
Range	30–85	
Sex		
Male	43	37
Female	75	63
Relation to patient		
Partner	96	81
Father/mother	1	1
Son/daughter	16	14
Sibling	4	3
Friend	1	1

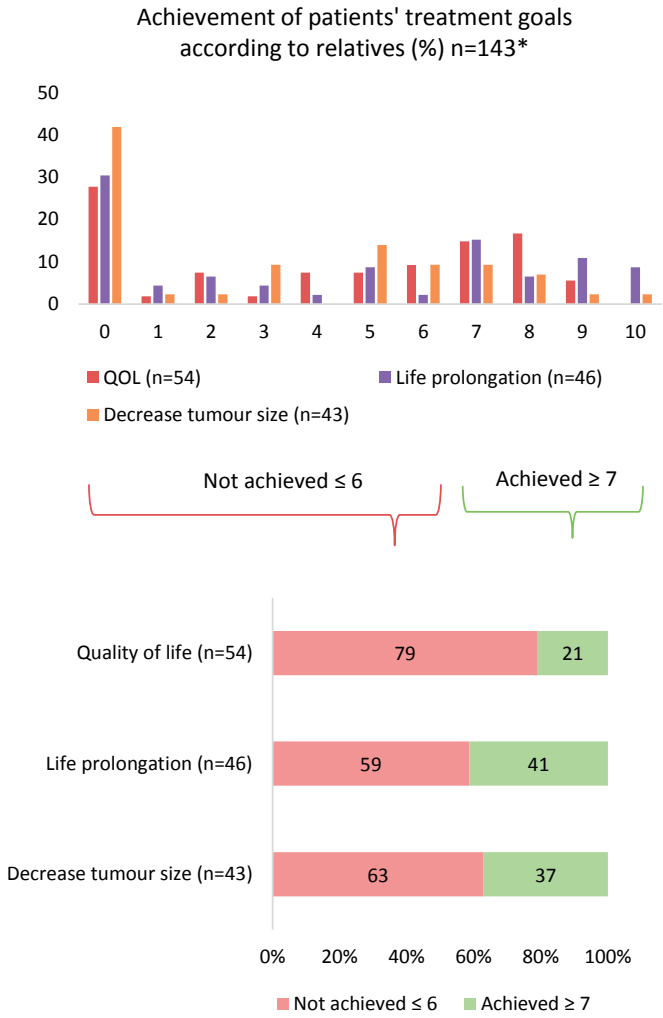

Figure 2. Achievement of the patients' treatment goals according to relatives on a scale from 0 to 10 with 0 meaning 'not achieved at all' and 10 meaning 'totally achieved'. These number are dichotomized into achieved and not achieved with a cut off score of 7. * Relatives (n=118) had answered on 143 treatment goals together.

In total, 76 relatives (64%) perceived none of the goals as achieved, 42 relatives (36%) reported that at least one of patients' goals was achieved, and 29 relatives (25%) reported that all goals were achieved (data not shown).

Satisfaction with patients' choice to start treatment

A total of 78% (n=92) of the relatives was, in hindsight, satisfied with the patients' choice to start treatment, 14% (n=16) was not satisfied about the treatment choice and 9% (n=10) was not sure.

When asked to explain why they felt satisfied or not with the patients' treatment choice, 42% of relatives reported only positive aspects, 31% reported both positive and negative aspects and 27% reported only negative aspects. Relatives that were satisfied with the treatment choice did not only mentioned positive aspects: 30% mentioned both positive and negative aspects and 22% mentioned only negative aspects. Furthermore, relatives that were not satisfied did not only mentioned negative aspects: 36% mentioned both positive and negative aspects and 20% mentioned only positive aspects.

The most frequently mentioned positive aspects were 'we tried everything' (24%), 'it was the patient's choice' (14%), and 'the patient lived longer' (14%). 'It was the patient's choice' was more frequently mentioned by relatives that were not satisfied with the treatment choice than relatives that were satisfied (23% versus 12%). 'The patient lived longer' was more frequently mentioned by relatives who were satisfied than relatives who were not (16% versus 4%). The most frequently mentioned negative aspects were 'the treatment did not work' (19%), 'there were side effects' (13%), and 'it was not my choice' (10%). Next to positive and negative aspects relatives also mentioned other aspects, which were often related to the quality of care. Insufficient quality of care was more frequently mentioned by relatives who were not satisfied than relatives who were (23% versus 10%). Good quality of care was only mentioned by relatives that were satisfied (21%) (table 2). Most of the relatives (78%) were satisfied with the choice to start a treatment (n=92). From the relatives who reported that at least one of patients' goals was achieved (n=42), 93% were satisfied about the treatment choice. When none of the goals were achieved (n=76), 70% of the relatives were satisfied.

Examples of explanation of relatives who answered 'satisfied about the treatment choice' and mentioned:

- **Only positive aspects:**
  *You try to get hope with the treatment. He had no side effects, as with chemotherapy. However, he progressed after a couple of cycles. We started the treatment to stall/extend. Every 3 weeks. Eventually he passed away through euthanasia, he wanted to keep control in his own hands (**in the categories 'It gives hope' and 'no side effects; relative of deceased patient, age between 50 and 60 years**).*
- **Positive and negative aspects**:
  *It was my husbands' choice, so that is good. But for me, it all went really fast. Doctors repeatedly said: it is going fine. Then, after surgery on his chest wound it suddenly went wrong and he quickly past away. It is really unfortunate/a shame, and I was angry, because we did not speak the oncologists when my husband was admitted to the hospital. No call, no visit. We had to hear from the ward doctor that there were no treatment options left and he would have very short time left (to live). But, he still had a good summer after the immunotherapy so that is nice (**in the categories 'It was the patients' choice', 'good quality***

Table 2. Positive and negative aspects mentioned by relatives on patients' choice to start treatment

N column (%)	Total (n=118) N (%)	Satisfied (n=92) N (%)	Not satisfied* (n=26) N (%)
Relatives mentioned: **			
• Only positive aspects	47 (42)	42 (48)	5 (20)
• Positive and negative aspects	35 (31)	26 (30)	9 (36)
• Only negative aspects	31 (27)	19 (22)	11 (44)
Positive aspects mentioned			
• We tried everything	28 (24)	22 (24)	6 (23)
• It was the patients' choice	17 (14)	11 (12)	6 (23)
• Lived longer	16 (14)	15 (16)	1 (4)
• The treatment worked	14 (12)	11 (12)	3 (12)
• No side effects	12 (10)	10 (11)	2 (8)
• It gives hope	10 (8)	7 (8)	3 (12)
• Good quality of life	6 (5)	6 (7)	0 (0)
• Other	3 (3)	3 (3)	0 (0)
Negative aspects mentioned			
• The treatment didn't work	23 (19)	17 (18)	6 (23)
• Side effects	15 (13)	11 (12)	4 (15)
• It was not my choice	12 (10)	5 (5)	7 (27)
• Quality of life worsened	10 (8)	3 (3)	7 (27)
• Treatment was given too long	9 (8)	4 (4)	5 (19)
• Burdensome hospital visits	5 (4)	3 (3)	2 (8)
• The treatment was started too late	4 (3)	4 (4)	0 (0)
Other aspects mentioned			
• Good quality of care	19 (16)	19 (21)	0 (0)
• Insufficient quality of care	15 (13)	9 (10)	6 (23)
• It was the choice of the oncologists	13 (11)	11 (12)	2 (8)
• I don't know how it would have been otherwise	7 (6)	3 (3)	4 (15)
• It helped science	3 (3)	3 (3)	0 (0)

*Including relatives who reported "not sure" on the treatment satisfaction.
** 4% missing. Percentages don't add up to 100% since more answers were possible.

***of life' and 'insufficient quality of care'; relative of deceased patient, age between 60 and 70 years**).*

- **Only negative aspects:**
  *In the final period we had our doubts. The exams took long and in the meantime the cancer kept growing in the liver. After 3 months of radiation of the lungs nothing happened. In the medical files it said palliative chemotherapy, however, this was not mentioned to us (curative). Chemotherapy is still junk, in hindsight the last chemotherapy was too much (**in the categories 'The treatment was started too late' 'insufficient quality of care' and 'treatment was given too long'; relative of deceased patient, age between 40 and 50 years**).*

Examples of relatives who answered 'not satisfied about the treatment choice' and mentioned:

- **Only positive aspects:**
  *It was his choice. He lived longer because of the chemo. His wife wanted to try. But at a certain point he did not want to anymore, also no immunotherapy unless it was possible from home (**in the categories 'Lived longer' and 'choice of the patient'; relative of deceased patient, age between 50 and 60 years**).*
- **Positive and negative aspects:**
  *My husband was so ill and he already received so many treatments. There were no more treatment options left, he felt like a test subject, it is tough, traveling long distance and we kept going/continued too long. In [other hospital] they also continue treatment for a long time. But everyone tries to grab on every straw/chance (**in the categories 'We tried everything', 'quality of life worsened', 'insufficient quality of care' and 'burdensome hospital visits'; relative of deceased patient, age between 70 and 80 years**).*
- **Only negative aspects:**
  *It didn't work. She still had lots of treatments after this one. From the chemo she only lost her hair/ turned balled (**in the categories 'The treatment didn't work' and 'side effects'; relative of deceased patient, age between 60 and 70 years**).*

Discussion

Relatives reported the goals 'quality of life', 'decrease tumour size' and 'life prolongation' as achieved in 21%, 37% and 41% respectively. Most of the relatives (78%) were satisfied about the patients' choice to start treatment. Even if none of the goals were achieved, 70% of the relatives were satisfied. In total, 52% of relatives who were satisfied with the patient's choice mentioned negative aspects of the treatment choice, such as the treatment did not work, that there were side effects or that it would not have been the relatives choice. While 80% of relatives who were not satisfied with the patient's choice to start treatment mentioned negative aspects. The most mentioned positive aspects were that they tried everything and that it was the patient's choice. In total, 31% of relatives reported both positive and negative aspects of the treatment choice, independently of being satisfied or not.

Relatives consider patient's treatment goals less often achieved than patients.
The patients for whom the relatives reported whether the treatment goals were achieved reported their predefined treatment goals 'quality of life', 'decrease tumour size', and 'life prolongation' achieved in 30%, 26% and 49% respectively.[10] Thus, compared to patients, relatives consider the goals 'quality of life' (21% vs 30%) and 'life prolongation' (41% vs 49%) less often achieved and 'decrease tumour size' (37% vs 26%) more often achieved. This difference could firstly be due to the fact that relatives reported the achievement of

goals after the patient died taking into account the whole illness. For the goal 'quality of life', for example, it might be that at the time the treatment stopped (the time point that the patient reported the achievement of goals) the quality of life of the patient was higher compared to the last phase of life. The latter was most likely the reference point for relatives when they considered whether the goal 'quality of life' was achieved. Secondly, relatives may have a different perspective on quality of life because they have their own believes and considerations to undergo or forgo cancer treatment than patients. Thirdly, they do not have the disease themselves, which may also influence their perspective. Fourthly, when looking at the negative aspects, relatives mentioned side effects and worsened quality of life. It might also be that from the perspective of relatives it is very difficult seeing their loved one deteriorate and suffer and therefore more often report the goal 'quality of life' as not been achieved. Finally, it is known that relatives tend to assess a patient's quality of life as somewhat lower than what the patient perceives.[20, 21]

Satisfaction with treatment decision is linked to negative feelings about treatment decision. Most of the relatives were, in hindsight, satisfied about the patients' choice to start treatment (78%), even if none of the goals were achieved (70%). These results are comparable to the patients' and oncologists' view regarding making the right decision to start treatment (patients: 79% and oncologist: 96%) even if none of the goals were achieved (patients: 72% and oncologists: 93%) in the previous study of Mieras et al.[10] it is known that measuring satisfaction is not without problems. It holds the risk of creating a positive bias which could, for instance, be influenced by the desire to give a socially desirable answer or, according to cognitive dissonance theory, a tendency to assess one's situation or actions as good in hindsight.[22, 23] Nevertheless, the fact that we found over half of people who were satisfied with the treatment decision described negative aspects related to the decision taken shows that satisfaction does not encompass the relatives' entire experience. The most mentioned negative aspects were that the treatment did not work and that there were burdensome side effects of the treatment. These negative aspects should be taken into account when deciding to start a treatment with a relatively low chance of success and high chance of side effects e.g. by managing expectations of patients and relatives with clear communication and highlighting the option of palliative or supportive care to treat side effects.

Next to negative aspects related to the treatment decision taken, many relatives also mentioned positive aspects. It was most frequently mentioned that it was positive the patient tried everything. Previously, we found that this was also an important aspect for the patients and oncologists.[10] Additionally, it was important for many relatives that the patients' wish for treatment was followed, even when the relatives themselves felt that the treatment might have gone on for too long. Notably, none of the positive aspects we found resonated with aspects valued at the end of life found in a study by Steinhauser et al.: 'pain and symptom management', 'clear decision making', 'preparation for death' and 'completion' valued at the

end of life.[8] This might be related to the fact that in our study we focused on the evaluation of the decision to start systemic treatment. For patients who start with treatment and their families, it might be more difficult to prepare for death than for people who do not start treatment. It might also be that they value the aspects at the end of life less.

Strengths and limitations

A strength of this study is that it provides new insights in the perspective of the relative on the treatment for an incurable disease of their loved one; we could not find studies which results we could compare to ours. Furthermore the contribution of both one academic and five non-academic hospitals (multi-centre and a case mix of patients) and the adequate number of participants at a difficult time willing to share information on a sensitive subject contribute to the validity of the results. Another strength is that through the structured telephone interviews with open questions, the relatives were allowed to elucidate positive and negative aspects on the treatment satisfaction. Since all interviews were conducted by one researcher continuity is assured, however, it may also cause interpretation bias which can be seen as a limitation. Another limitation might be that the researcher wrote down the answers during the telephone interview and might not have managed to capture all the details, instead of when the conversations were audio recorded.

Conclusions

The majority of relatives reported patients' treatment goals as not achieved. However, relatives were predominantly satisfied about the treatment choice. Satisfaction of treatment choice does not encompass the entire experience with the treatment decision since the majority of relatives mentioned negative aspects of this decision. At the time of making the treatment decision it is important to manage expectations about chance of success and possible side effects of the treatment. Relatives, like patients, find it important to feel that something is being done, thus, it can be beneficial to not contrast the option of systemic treatment with the option of doing nothing. Palliative care can also be framed as a treatment option.

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7

GENERAL DISCUSSION

The overall aim of this thesis is to gain more insight into systemic treatment for patients with metastatic lung cancer in the context of the end of life. Research aims are to study:

- The percentage of metastatic lung cancer patients who receive chemotherapy or TKIs in the last month of life in the Netherlands.
- The percentage of metastatic lung cancer patients who die inside the hospital and whether hospital death is associated with receiving systemic treatment in the last month of life.
- The type and feasibility of treatment goals that patients and their oncologists have when starting systemic treatment.
- To what extent patients' and oncologists' treatment goals are achieved after systemic treatment and whether this differs between types of therapy. In addition, whether it was the right decision to start treatment in hindsight.
- The perspective of the relatives in hindsight on the achievement of the patients' treatment goals and whether they are satisfied about the patients' treatment choice.

This final chapter will discuss the findings of the studies described in the previous chapters. Firstly, some methodological considerations will be formulated. Secondly, the main findings of the previous chapters and the interpretation of the results will be discussed. Finally, several implications of this thesis for clinical practice and future research will be considered.

Methodological considerations

To answer the objectives of this thesis two studies were conducted: a multicentre **retrospective patient file study** in ten hospitals in the Netherlands (chapter 2 and 3) and a multicentre prospective **longitudinal questionnaire study** in patients, their oncologists and their relatives in six hospitals in the Netherlands (chapter 4 – 6).

Retrospective patient file study

The patient file study performed in ten hospitals in the Netherlands included 1322 files of patients diagnosed with metastatic lung cancer who died between 2013 and 2015. The data from this study was collected retrospectively.

A strength of this study is the high number of patients analysed (n=1322) across ten different hospital sites; this makes the results robust and generalizable. By including 3 academic hospitals and 7 non-academic hospitals distributed across the North, East, South and West of the Netherlands, we assume that it is a representative sample of the Dutch metastatic lung cancer population. Selection bias is minimized because all patients diagnosed with metastatic lung cancer were included in this study, assuming that diagnose codes were administered correctly and that all patients with lung cancer have a file in their hospital.

However, this study has some potential limitations. The inevitable limitation of a patient file study is that the files are the only source of information. Therefore, false information is hard to detect and missing values cannot be filled up. Also, some files may be incomplete because patients went to another hospital for care. Specifically for our study, we were able to extract the information on the systemic treatment patients received, however, we were unable to discover the rationale behind the patient's and the oncologist's choice to start and stop chemotherapy or TKIs. We had information on several possible covariates or confounders, but this was not complete. For instance, data on performance status could not always be retrieved from medical records due to the absence of documentation. Patients with a poor performance status might have a higher risk of hospitalization and consequently, hospital death. Other potentially relevant covariates or confounders are symptom burden, date of diagnosis, ethnicity and socioeconomic circumstances, among others. Lastly, we only documented the last systemic treatment line, therefore we have no knowledge on how many or which systemic treatments patients received in earlier treatment lines.

Longitudinal questionnaire study

The longitudinal questionnaire study was performed between November 2016 and April 2018. We included 266 patients with metastatic lung cancer who received a systemic treatment (chemotherapy, immunotherapy or targeted therapy with tyrosine kinase inhibitors (TKIs)), in either an academic or a non-academic hospital in the Netherlands. We chose a longitudinal design to follow the patients throughout their disease course and ask them to what extent they feel their goals were achieved and whether it was a good decision to start a systemic treatment in hindsight. Additional semi-structured interviews were performed with 15 metastatic lung cancer patients and 5 treating oncologists from one academic hospital.
One part of the longitudinal questionnaire study was a structured telephonic interview to gain insight into the perspective of the relatives on the systemic treatment for an incurable disease of their loved one. We conducted telephonic interviews between February 2017 and November 2019 including 118 relatives of deceased metastatic lung cancer patients who started a systemic treatment in either an academic or a non-academic hospital in the Netherlands and who completed the questionnaire on their treatment goals before start of the systemic treatment.

Strengths of this study are the large sample size of patients, the case mix of both one academic and five non-academic hospitals, the use of open ended questions so that patients and oncologists had to formulate the treatment goals in their own words and the additional semi-structured interview to better understand respondents answers. Also, because both patients and oncologists filled out a questionnaire simultaneously but independently from each other, the answers to the questionnaires could be compared between patients and oncologists. We asked the patients and oncologists to fill out the questionnaire immediately

after the systemic treatment started and therefore limited any recall bias, whereas other studies mostly ask about treatment goals in retrospect.

A strength of the interview study is that we gained information on all patients, including patients who were not able to fill out the questionnaire after treatment due to rapid progression of the disease or sudden death. In this way we have information on the disease process of 118 patients in the period between the ending of the systemic treatment and death.

A limitation is that in the semi-structured interview study, we only interviewed patients and oncologists from the academic hospital, possibly giving bias to the additional information. These patients are a selective group who more often than in non-academic hospitals wish to start a systemic treatment. The questionnaire on treatment goals was written in Dutch; therefore, only Dutch-speaking patients could participate. This resulted in a cohort of patients with mostly a Dutch cultural background, while it is known that people with a migration background sometimes have other views on treatment decisions in the last phase of life.[1,2] About 15 non Dutch-speaking patients were excluded for participation on this ground. We did not receive all questionnaires after systemic treatment since some patients died during the treatment; In other cases, the disease progressed so rapidly there was no time to ask the patient to fill out the questionnaire after treatment. Therefore, only the patients with a relatively stable condition filled out the questionnaire after the systemic treatment, which may result in higher treatment goal achievement scores. However, we do have the questionnaires from the oncologists of the patients who died and did not fill out the questionnaire so information on this patient group is available.

A limitation of the interview study was that the interview was on average about three months after the patient died and on average over half a year after the last systemic treatment the patient received. The long time between these events and the interviews might create recall bias resulting in different views over time. Also, views on treatment might be emotionally loaded because of the last phase of life.

An overall limitation of both studies is that due to rapid evolvements in systemic treatments the current guidelines have been changed. The analysis of the patient file study is somewhat outdated with the introduction of immunotherapy and the analysis of the longitudinal questionnaire study is outdated with the combination of chemotherapy and immunotherapy as current guideline. Analysis of current data might yield different results, however, these results are still valuable and give insight into systemic treatments at the end-of-life.

Main findings and interpretation of the results

The main findings in this thesis are that:

- 18% of metastatic lung cancer patients received chemotherapy (11%) or TKIs (7%) in the last month of life. Of the patients who received chemotherapy in the last month of their life, 54% started this systemic treatment in the last month of life,
- 18% of metastatic lung cancer patients died in the hospital and in-hospital death was associated with a relatively late use of chemotherapy or targeted therapy,
- patients and oncologists set various goals for the systemic treatment they receive/ prescribe; respectively: 'quality of life' (45%; 72%), 'life prolongation' (45%; 55%), 'decrease in tumour size' (39%; 66%) and 'cure'(19%; 2%), with patients having slightly higher feasibility scores on their treatment goals compared to oncologists (6.8 vs 5.8 on a 10-point scale),
- most goals patients and oncologists had when starting a systemic treatment were not achieved after treatment; the goals 'quality of life', 'life prolongation', 'decrease in tumour size' and 'cure' were achieved in 30%, 49%, 26% and 44% for patients and in 37%, 41%, 44% and 0% for oncologists, respectively. Additionally, 79% of patients and almost all oncologists (96%) felt, in hindsight, that they had made the right decision to start the treatment, even if they had not achieved their goals, with the main reason that 'doing something' was important,
- compared to patients, relatives consider the goals 'quality of life' (21% vs 30%) and 'life prolongation' (41% vs 49%) less often achieved and 'decrease tumour size' (37% vs 26%) more often achieved. Most relatives (78%) were satisfied with the patients' choice to start a systemic treatment, even if none of the goals were achieved (70%). However, satisfaction with the treatment choice does not always cover the entire experience. Aside from positive aspects related to the decision to start a systemic treatment, many relatives also mentioned negative aspects, like 'the treatment did not work'.

Receiving a systemic treatment at the end of life

The retrospective patient file study showed that 18% of metastatic lung cancer patients received a systemic treatment in the last month of life (11% chemotherapy and 7% TKIs). The percentage of patients receiving chemotherapy in the last month of life is comparable to percentages found for patients with lung cancer in other studies.[3-10] For patients receiving TKIs in their last month of life, we showed that 71% did not carry a targetable driver mutation. TKIs are said to have less life threatening side effects compared to chemotherapy, lead to fewer hospital visits and show a rapid response.[11-18] However, the response rate is low in patients without a targetable driver mutation and non-life threatening side effects are common, so it is debatable whether this should be considered good practice.[19] The downside of these systemic treatments, especially chemotherapy, are the severe adverse events, which decrease

the patient's quality of life.[12,20-22] Cancer immunotherapy was only introduced in 2015, thus our study did not include patients who were treated with immunotherapy. However, a more recent study shows that 27% of palliative cancer patients who received immunotherapy, received this treatment in the last 30 days of life.[23]

Additionally, we found that out of the patients who received chemotherapy in the last month of their life, 54% started this treatment in the last month of life. In the interviews of the longitudinal questionnaire study, we observed that patients start a systemic treatment because they want to do everything to fight the disease and it gives them a form of hope. This has also been shown in other studies.[24,25] Furthermore, starting a systemic treatment may be a coping strategy for patients to deal with their approaching death. Buiting et al. reported that some patients regard chemotherapy-free periods to be more stressful than periods of treatment.[26] The semi-structured interviews and other studies show that oncologists may offer further treatment and strive for life prolongation since they might need to feel like they have to do something.[27] This was seen in a study of Van Leeuwen et al., oncologists preferred to continue a systemic treatment rather than withhold it despite doubts that the treatment benefits actually outweigh the burdens.[28]

The patient file study also showed that 18% of metastatic lung cancer patients died in the hospital and in-hospital death was associated with the relatively late use of chemotherapy or targeted therapy. This result confirms findings from earlier studies that receiving chemotherapy in the last month of life is associated with a reduced likelihood of home death.[22,29,30] Regarding hospital deaths, it was shown that in 2008 28% of lung cancer patients died inside the hospital in the Netherlands.[31] However, the number of hospital deaths in the Netherlands is relative low compared to the rest of the world, with a large variation across countries from 26% (Netherlands and New Zealand) to 87% (South Korea).[32] Knowledge about these numbers are informative since place of death is often regarded as an important parameter for quality of care.[33] Literature shows that most patients prefer to die at home[33-38] and satisfaction with end-of-life care is improved when patients die in their preferred location.[39] It has been shown that receiving systemic treatments shortly before death may result in potential burdensome and increased hospital admissions and consequently hospital deaths, which could be a threat to good end-of-life care.[40-42]

Treatment goals of patients and oncologists for starting a systemic treatment

In the previous paragraphs we showed that a substantial percentage of metastatic lung cancer patients received a systemic treatment, even close to death, which could be seen as aggressive end-of-life care. However, in the longitudinal questionnaire study we see that patients are intrinsically willing to start these treatments. When asking about the goals of treatment, patients and oncologists reported 'quality of life' (45%; 72%), 'life prolongation' (45%; 55%), 'decrease in tumour size' (39%; 66%) and 'cure' (19%; 2%) respectively. These

results in combination with the semi-structured interview study show that patients may choose intensive systemic treatment that might have limited benefits and major toxicity in order to try anything that might improve their quality of life or prolong their life, which is also shown in literature.[43,44]

Although 82% of patients reported discussing their treatment goals with their oncologists and 91% of oncologists reported discussing goals with their patients, we found low concordances between patients' and oncologists' goals: with 24% for 'decrease in tumour growth' and 37% for 'quality of life'. A recent study by Douglas et al. showed that patients with advanced cancer and their oncologist also had a low concordance on the goals 'survival' (8.3%) and 'quality of life' (15%).[45] Other studies found much higher rates of patient-oncologist concordance in treatment goals ranging between 68% and 72%.[46-48] However, these studies consisted of a heterogeneous cancer population with various disease stages. We found multiple possible explanations for the low concordance out of the semi-structured interviews and literature. First, it might be that there is discrepancy in the importance of patients' and oncologists goals and therefore in the goals they remember to have discussed. Second, it is possible that an oncologist does not emphasize the direct goal in the questionnaire but more the ultimate goal in the discussion with the patient (or vice versa). Third, oncologists might not want to mention goals that are not feasible because it would discourage the patient and cause emotional distress. Fourth, oncologists may use complex language and report treatment goals to patients in an euphemistic and optimistic manner. Fifth, despite clear communication from the oncologist regarding their view on the treatment, patients might not be able to fully process the information or they might interpret the aim of the treatment more positively than it was intended. It is well known that patients poorly absorb information after being diagnosed with a life-threatening disease. However, it might also be that patients and oncologists actually had different goals, without misunderstanding.[49-54]

The longitudinal questionnaire study also showed that patients had slightly higher feasibility scores on their treatment goals compared to oncologists (6.8 vs 5.8 on a 10-point scale). From the interviews, it appeared that most patients mentioned hope as an explanation for a high feasibility score before treatment. This might also explain the rather high feasibility score of 7,0 for the treatment goal cure. It became clear that oncologists may also influence hope; their willingness to start a systemic treatment fed patients' hope for cure or life prolongation as seen in the interviews. Other studies also showed that patients were more optimistic about their prognosis and treatment goals compared to their oncologists.[55,56]

Achievement of treatment goals and the right decision to start a systemic treatment in hindsight

The treatment goals that were defined by patients and oncologists when starting a systemic treatment were 'quality of life', 'life prolongation', 'decrease in tumour size' and 'cure'.

According to patients these were achieved in 30%, 49%, 26% and 44% respectively, according to oncologists in 37%, 41%, 44% and 0% respectively and according to relatives in 21%, 41%, 37% and 0% respectively. No difference was found between the type of systemic treatment and treatment goals.

The goal 'decrease in tumour size' was rarely reported as achieved by the patients (26%) and less often reported compared to the oncologists (44%) and relatives (37%). It could be that oncologists and relatives report this goal as achieved with a small decrease in tumour size, while patients only consider a substantial decrease as achievement of this goal. It may also be that a goal focussed on fighting the cancer is linked to other goals in the minds of patients but not overtly expressed. This could indicate that goals might be hierarchical, with lower order goals serving to achieve more important higher order goals. However, more importantly, this specific goal might not seek the specific end of decreasing the tumour size but serve as a reason to do everything that is possible to fight the disease.

Patients and oncologists perceived the goal 'quality of life' as achieved in 30% and 37% respectively, while according to relatives, this goal was achieved in only 21%. A possible explanation might be that the side effects of the treatment actually decreased the quality of life in most cases.[12,20-22] This is alarming because quality of life is regarded as most important in the last phase of life and it highlights that communication between patients and oncologists about the treatment goals and their feasibility is hugely important. It might also be that from the perspective of relatives, it is very difficult seeing their loved one deteriorate and suffer and, therefore, more often report the goal 'quality of life' as unachieved. Overall, it is known that relatives tend to assess a patient's quality of life as somewhat lower than the patients' assessment.[57,58] However, patients with a higher score on their quality of life questionnaire more often perceived their treatment goals as achieved; not only the goal 'quality of life', but also the other goals. It is logical that patients with higher quality of life more often perceive their goals as achieved as they probably feel better.

Interestingly, from the 27 patients who had 'cure' as treatment goal, 44% (12 patients) reported this goal as achieved. This goal is unrealistic since metastatic lung cancer cannot be cured. In the previous paragraph we mentioned that for patients hope can play an important role in setting 'cure' as a treatment goal, therefore, hope could be a coping strategy. However, when asking about the achievement of the goal 'cure' in the interviews, one patient answered 'the oncologists said that the scan was good'. It seems that this patient misunderstood the message of the oncologist, since he or she was not cured. This emphasizes the necessity of communication with specific discussions on systemic treatments with palliative intends instead of curative intend.

The achievement of treatment goals when using Tyrosine Kinase Inhibitors (TKIs) is a topic worth to discuss. From the retrospective patient file study, we concluded that a substantial percentage of metastatic lung cancer patients received TKIs. However, in the longitudinal questionnaire study, we saw that most of the treatment goals that patients had were not achieved when they were treated with TKIs. If we look at the treatment goals for different systemic treatments received, we see that most patients who received TKIs reported 'quality of life' as a goal. TKI's are often seen as a promising treatment, due to less life threatening side effects and a higher response rate compared to chemotherapy. Therefore, patients might hope for an increase in quality of life with this treatment.[59] However, higher expectations might lead to more disappointment and lower achievement scores. The continuation of TKIs towards the end of life may be due to an overestimation of the likelihood of survival and underestimation of side effects by oncologists. It might also be a result of the fact that it is often easier to recommend a new line of treatment than to discuss cessation of treatment.[60,61] Alternatively, it may also be attributed to the disease flare associated with the discontinuation of TKIs.[11] Therefore, patients might hold unrealistic expectations of new treatment options and cherish even small survival benefits.[43]

In hindsight, 80% of patients felt that they sufficiently discussed their goals at the start of treatment with their oncologists. This number is much higher compared to a study by El-Jawahri et al. where only 22% of patients reported discussing their wishes with their oncologists.[62] Additionally, 79% of patients, almost all oncologists (96%) and 78% of the relatives felt, in hindsight, that they had made the right decision to start treatment, even if they had not achieved their goals. The qualitative interviews showed that wanting to do 'something' was important for both patients and oncologists when justifying that starting treatment was the right decision. However, satisfaction with the treatment choice does not always cover the entire experience. More than halve of relatives who were satisfied also mentioned that the treatment did not work, that there were side effects or that it was not their choice. These negative aspects should be taken into account when deciding to start a systemic treatment with a low chance of success and high chance of side effects. One possible way to do this is by managing expectations of patients and relatives with clear communication and highlighting the beneficial potential of palliative care to treat symptoms of the cancer. It also has been shown that when patients had end-of-life discussions, bereavement adjustment for families was better.[63]

Interpretations of the results

This thesis shows that a substantial number of metastatic lung cancer patients receive a systemic treatment in the last month of life and that both patients and oncologists are intrinsically motivated to start a treatment to try everything to fight the disease. Even if treatment goals are not achieved, most of the patients and oncologists are satisfied with the decision to start the treatment. The question arises whether the 'start treatment to do

something' approach is the best option for these palliative patients or that alternative options such as palliative care are more suitable. Multiple studies have evaluated systemic treatments at the end of life and receiving and even starting chemotherapy in the last month of life is generally seen as aggressive care. It often goes along with more visits to the emergency department and the intensive care unit and consequently more hospital deaths.[6,22, 64-67] Therefore, in 2012 the American Society for Clinical Oncology (ASCO) recommended palliative care to avoid the use of chemotherapy at the end of life and to improve patient care.[68,69] However, we found that after this recommendation was published, there is still a substantial percentage of patients receiving chemotherapy or TKIs in the last month of life.

Early palliative care (EPC) means early integration of palliative care c.q. care that is provided from diagnosis throughout the continuum of care. It consists of consultation with palliative care experts, advance care planning (ACP) and shared decision making (SDM).[70-74] Since its introduction multiple studies have shown an association with a decreased use of chemotherapy at the end of life in metastatic lung cancer patients.[72-79] Early integration of palliative care also enhances patients' understanding of their illness and prognosis.[80-82]

Part of early palliative care is the discussion of treatment goals, which may increase patient-oncologist communication, enabling patients to better identify and explain their treatment preferences and helping oncologists act according to those preferences.[72,73,76] The fact that the results in the questionnaire study show that 19% of metastatic lung cancer patients reported 'cure' as a treatment goal, makes it questionable how well these goals have been discussed. However, in the semi-structured interview study most of the patients who mentioned 'cure' as a treatment goal reported this goal not as highly realistic. Outlining realistic goals that patients and families can look forward to may assist in maintaining hope in light of a life-threatening illness. Evidence demonstrates that early discussion of treatment goals in advanced cancer patients is associated with beneficial outcomes for patients resulting in potential cost savings.[63,72,83]

Palliative care cannot be optimal without open and clear discussions regarding the patients' preferences. **Advance care planning (ACP)** is a dynamic and ongoing process to discuss patients' values, goals and hopes and identify their future healthcare preferences. The objective of advance care planning is to make sure that possible treatments align with patient's wishes. This can be done by determining the overall goal of medical care and discuss the interventions that should and should not be provided.[84] Another important aspect of palliative care is the location in which patients wish to receive this care and the location in which they wish to die. ACP might help patients to gain insight into these wishes and timely discuss it with their treating physician.[85]

Shared decision making (SDM) is an approach in which patients and oncologists discuss the best available evidence when facing decisions, while patients are assisted in expressing their preferences and become actively involved in decision making.[86,87] SDM is seen as an important element of high quality cancer care with essential elements including patients' values and understanding of treatment goals[88-90] and is associated with improvements in patient satisfaction.[91] For this type of decision making it might be beneficial to educate and train oncologists in communication around difficult clinical situations, using a conversation guide or a checklist to discuss treatment goals.[76,92-95] Key elements that should be addressed are the understanding of the prognosis and the treatment goals. It is important to consider if starting systemic treatments that are unlikely to achieve treatment goals are in the best interest of patients. Thus, in patients with a low chance of responding positively to a systemic treatment, the focus should be put on improving their quality of life.

Additionally, it could be helpful to make use of a **decision aid (DA)** in shared decision making.[96] Decision aids are tools that help patients to come to the best decision by showing the available treatment options, clarifying values and providing information about the available options and their outcomes.[97] DAs are available in various forms such as patient letters, videos, leaflets or computer programs to encourage patients to think about their treatment preferences.[98] DAs for metastatic lung cancer patients might be promising when asking patients about their treatment goals in an open-ended way allowing them to describe their goals and reveal patients' beliefs, values and preferences. Oncologists are then able to clarify and confirm patients' goals, discuss the clinical implications of these goals, determine whether all relevant goals have been considered and set priorities among goals when necessary, as recommended by Haberle et al.[99]

In conclusion, for patients with a life-threatening disease, early palliative care is important to concurrently treat the tumour as also the patient with the disease. This approach may result in improvement in symptom control and a carefully-weighed treatment decision that is closely related to the patients' wishes.

Implications for clinical practice

Based on the interpretation of the results we highly recommend the implementation of early palliative care to avoid aggressive end-of-life care in metastatic lung cancer patients and give care aligned with the preferences of the patient. An important aspect of early palliative care are end-of-life discussions about the goals patients have for their systemic treatment. Before deciding on the treatment, there should be substantial discussions regarding the treatment options, their benefits and side-effects and the goals patients have, allowing physicians to align treatments with what is most important and realistic to the patient. Strategies to normalize end-of-life discussion as part of clinical practice, including decision aids and methods for early and continuous assessment of patients' goals are necessary.[100] Based on the results

presented in this thesis we designed factsheets for metastatic lung cancer patients and their treating oncologists (in Dutch) which could also be helpful in having these discussions.[101,102] These goals should be regularly evaluated and discussed from diagnosis on through the entire treatment trajectory to discuss how realistic these goals are. When treatment goals are no longer realistic or unachievable, oncologists should communicate this with patients and potentially withdraw the anticancer treatment, switching to palliative care alone. In addition to that, conversations about the preferred place of death should be integrated into end-of-life patient-oncologist conversations so that oncologists are aware of the patients' preferences concerning place of death. Palliative care experts can play a big and important role in these end-of-life discussions, concerning treatment goal evaluation and preferred place of death. This can be done in the way of early palliative care, i.e. that palliative care experts regularly have these discussions with metastatic lung cancer patients early in the disease trajectory, or by involving palliative care consultants when needed in certain cases. The latter option is probably more feasible in the Netherlands as every hospital in the Netherlands is obliged to have a palliative team to support among others oncologists in delivering end-of-life care and to have end-of-life discussions with patients at the end of life when needed.[100,101]

Recommendations for future research

In the previous paragraph, we recommended to implement early palliative care to avoid aggressive end-of-life care in metastatic lung cancer patients. This is based on the findings presented in this thesis that 18% of metastatic lung cancer patients received a systemic treatment in the last month of life. However, these results are derived from a retrospective patient file study containing metastatic lung cancer patients who died between 2013 and 2015. These patients are treated via treatment guidelines which are outdated compared to the current guidelines in the Netherlands, with the introduction of immunotherapy as second-line treatment for metastatic lung cancer patients since 2016 and the introduction of a combination of chemotherapy and immunotherapy as first-line treatment option since 2019.[103,104] Therefore, it would be interesting for future research to investigate the percentage of metastatic lung cancer patients who received a systemic treatment in the last month of life, which may generate different results compared to the results presented in this thesis. In the past decades, non-small cell lung cancer treatment had a breakthrough with Tyrosine Kinase Inhibitors (TKIs) targeted therapy.[105] During the research described in this thesis, systemic treatment with TKIs was still emerging, therefore we recommend to investigate the consequences of the use of TKIs, especially shortly before death. This could be done in the retrospective manner as we did, however, results would be even more valuable if semi-qualitative interviews would shed light on the rationale of starting and continuing TKIs (or other systemic treatments) in the last phase of life. Also, the amount of patients receiving TKIs in the last month of life and died inside the hospital could probably be investigated with higher numbers due to the increasing use of TKIs compared to the number reported in this thesis. These results would make it possible to consider whether not giving TKIs shortly

before death should be a quality indicator for appropriate end-of-life care, as is the case for chemotherapy.[29]

In the longitudinal questionnaire study we evaluated the treatment goals and patients' retrospective view regarding the decision to receive systemic treatment for their metastatic lung cancer. However, because we were interested in the views of patients who received a systemic treatment, we excluded patients who opted for no systemic treatment. It would be interesting to discover the rationale and the view regarding the decision of the patients who opted for no treatment and compare it with the results of the patients who received a systemic treatment.

Final remarks

This thesis shows that a substantial percentage of metastatic lung cancer patients starts a treatment near the end of life. Additionally, in-hospital mortality is high in patients who received a treatment in the last month of life, while home is most often the preferred place of death. This thesis also shows that patients and oncologists want to do everything that is possible to fight the disease, including aggressive treatments which might decrease the quality of life of patients and hinder them from preparing for death. We suggest to have continuous communication between the patient and oncologist throughout the disease progress, discussing the treatment goals and how feasible these goals are. Palliative care should be integrated at the time of diagnosis to improve this communication and the quality of life of the patients and their families facing problems associated with life threatening illness. This may prevent and relieve suffering through the early identification, correct assessment and treatment of physical, psychosocial or spiritual problems.

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Appendix 1. Factsheet for patients and relatives

Doelen van behandeling bij uitgezaaide longkanker (1)

Longkanker is kanker die in de longen is ontstaan. Helaas wordt deze diagnose vaak pas vastgesteld als de ziekte al uitgezaaid en niet meer te genezen is

1. Huidkanker
2. Darmkanker
3. Borstkanker
4. Longkanker

Longkanker is de 4e meest voorkomende kankersoort in Nederland

9 maanden tot 3 jaar

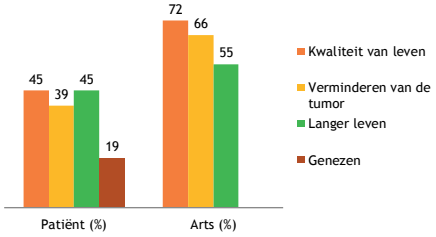
De meeste mensen met de diagnose uitgezaaide longkanker leven tussen de 9 maanden tot 3 jaar

Meer dan de helft van de patiënten met uitgezaaide longkanker start nog een medicamenteuze behandeling zoals bijvoorbeeld chemotherapie, immuuntherapie of doelgerichte therapie

- Onderdrukken de tumorgroei
- Verminderen symptomen van de tumor

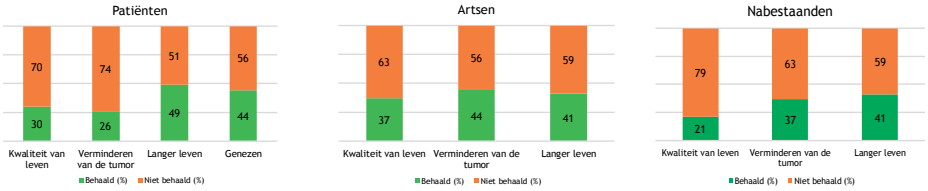
- Geven bijwerkingen
- Kunnen door bijwerkingen de kwaliteit van leven verminderen

Welke behandeldoelen hebben patiënten en hun artsen als ze besluiten te starten met een behandeling voor uitgezaaide longkanker



"Genieten"
"Minder pijn"
"Heel veel reizen"
"Uitzaaiingen tegengaan"
"Afremmen tumor"
"Mijn leven verlengen"
"Geboorte kleinkind meemaken"
"Beter worden"
"Hopen op een wonder"

Hoe vaak worden deze behandeldoelen behaald?



Vaak worden behandeldoelen van patiënten en artsen volgens henzelf en nabestaanden niet behaald. Dat het doel 'genezen' volgens patiënten behaald is, ook al zijn zij ongeneeslijk ziek, kan hoop of miscommunicatie zijn

Factsheet voor patiënten en naasten – Amsterdam UMC, 2020

Doelen van behandeling bij uitgezaaide longkanker (2)

Ook al worden doelen niet behaald, patiënten, artsen en nabestaanden zijn toch tevreden met de keuze om de behandeling te starten

Patiënten:

"Ik had geen keuze"
"Ik heb tenminste alles geprobeerd"
"Je weet niet hoe het anders was geweest"

79%

van de patiënten is tevreden met de keuze van de behandeling

3 van de 4

patiënten zijn ook tevreden als de doelen niet behaald zijn

96%

van de artsen is tevreden met de keuze van de behandeling

9 van de 10

artsen zijn ook tevreden als de doelen niet behaald zijn

78%

van de nabestaanden is tevreden met de keuze van de patiënt om te starten met behandelen

Nabestaanden zien terugkijkend zowel positieve als negatieve aspecten van de behandeling

\+

"Alles is geprobeerd"
"Het was de keuze van de patiënt"
"Mijn naaste heeft langer geleefd"

\-

"De behandeling is niet aangeslagen"
"Bijwerkingen"
"Het was niet mijn keuze"

Bespreek uw behandeldoelen met uw arts

Dit kan ervoor zorgen dat de behandeling die u ontvangt goed past bij uw behoeften en tegelijkertijd realistisch is

Schrijf bijvoorbeeld op wat voor u belangrijk is en bespreek dit in het volgende consult met uw arts

a. _____
b. _____
c. _____
d. _____

Deze factsheet voor patiënten is gebaseerd op gegevens uit het onderzoek "Beoogde en bereikte doelen van behandelingen in de laatste levensfase vanuit patiënten en artsen perspectief", uitgevoerd door Amsterdam UMC Amsterdam 2020. Zie ook https://palliatievezorgnoordhollandflevoland.nl/Projecten/Beoogde-en-bereikte-doelen

Dit onderzoek is gefinancierd door ZonMw en KWF kankerbestrijding

Appendix 2. Factsheet for health care professionals

Doelen van behandeling bij uitgezaaide longkanker (1)

Meer dan de helft van de patiënten met uitgezaaide longkanker start nog een systemische behandeling

- Onderdrukken de tumorgroei
- Verminderen symptomen van de tumor

- Geven bijwerkingen
- Kunnen door bijwerkingen de kwaliteit van leven verminderen

Patiënten kunnen een gelimiteerd idee hebben over hun prognose en behandelopties

Temel et al., 2011; Weeks et al. 2012

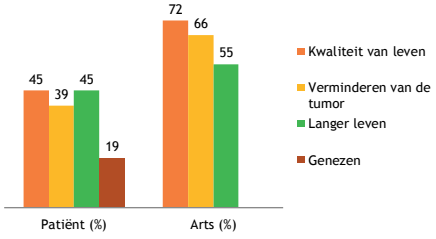
69%

begreep niet dat hun behandeling de kanker niet meer zou genezen Weeks et al. 2012, USA

14%

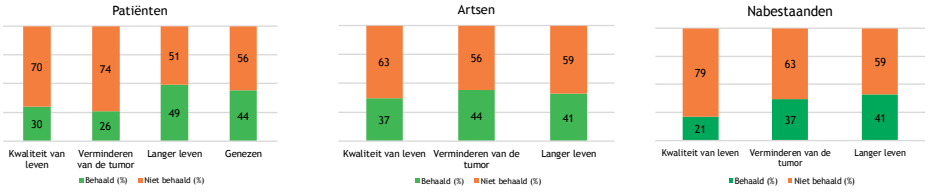
van longkanker patiënten zou niet opnieuw voor chemotherapie kiezen Visser et al. 2018, NL

Welke behandeldoelen hebben patiënten en hun artsen als ze besluiten te starten met een behandeling voor uitgezaaide longkanker



"Genieten"
"Minder pijn"
"Heel veel reizen"
"Uitzaaiingen tegengaan"
"Afremmen tumor"
"Mijn leven verlengen"
"Geboorte kleinkind meemaken"
"Beter worden"
"Hopen op een wonder"

Hoe vaak worden deze behandeldoelen behaald?



Vaak worden behandeldoelen van patiënten en artsen volgens henzelf en nabestaanden niet behaald. Dat het doel 'genezen' volgens patiënten behaald is, ook al zijn zij ongeneeslijk ziek, kan hoop of miscommunicatie zijn

Factsheet voor zorgverleners – Amsterdam UMC, 2020

Doelen van behandeling bij uitgezaaide longkanker (2)

Ook al worden doelen niet behaald, patiënten, artsen en nabestaanden zijn toch tevreden met de keuze om de behandeling te starten

Patiënten:

"Ik had geen keuze"
"Ik heb tenminste alles geprobeerd"
"Je weet niet hoe het anders was geweest"

79%

van de patiënten is tevreden met de keuze van de behandeling

3 van de 4

patiënten zijn ook tevreden als de doelen niet behaald zijn

96%

van de artsen is tevreden met de keuze van de behandeling

9 van de 10

artsen zijn ook tevreden als de doelen niet behaald zijn

78%

van de nabestaanden is tevreden met de keuze van de patiënt om te starten met behandelen

Nabestaanden zien terugkijkend zowel positieve als negatieve aspecten van de behandeling

\+

"Alles is geprobeerd"
"Het was de keuze van de patiënt"
"Mijn naaste heeft langer geleefd"

\-

"De behandeling is niet aangeslagen"
"Bijwerkingen"
"Het was niet mijn keuze"

Conclusies en aanbevelingen

- Doelen van patiënten en artsen worden vaker niet dan wel behaald – dit geldt het vaakst voor het doel 'kwaliteit van leven'
- De meeste patiënten, artsen en nabestaanden zijn achteraf tevreden met de keuze om te starten met een systemische behandeling, ook al is hun doel niet bereikt
- Patiënten en artsen vinden het vooral belangrijk 'iets' te doen en geen kansen te missen
- Het is belangrijk dat doelen van starten met systemische behandeling uitgebreid worden besproken om te komen tot een keuze die goed past bij de behoeften van de patiënt en tegelijkertijd realistisch is
- Mogelijk zijn er andere alternatieven binnen de palliatieve zorg voor het 'iets' doen dan starten met een systemische behandeling – zeker als het gaat om het bereiken van 'kwaliteit van leven'

Deze factsheet voor zorgverleners is gebaseerd op gegevens uit het onderzoek "Beoogde en bereikte doelen van behandelingen in de laatste levensfase vanuit patiënten en artsen perspectief", uitgevoerd door Amsterdam UMC Amsterdam 2020. Zie ook https://palliatievezorgnoordhollandflevoland.nl/Projecten/Beoogde-en-bereikte-doelen

Dit onderzoek is gefinancierd door ZonMw en KWF kankerbestrijding

8

SUMMARY
SAMENVATTING
DANKWOORD
ABOUT THE AUTHOR
LIST OF PUBLICATIONS

Summary

Chapter 1 provides an introduction to the topic of this thesis: treating metastatic lung cancer at the end of life. Lung cancer is currently one of the most frequently diagnosed cancers worldwide. Systemic treatments such as chemotherapy, immunotherapy and targeted therapy with Tyrosine Kinase Inhibitors (TKIs) aim to relieve symptoms with temporary disease control. However, it may also cause side effects which may lead to a decreased quality of life. A trend towards increasing use of systemic treatments for metastatic lung cancer has been shown, often called 'aggressive care'. Several studies have shown that treatment at the end of life may result in potential burdensome and inappropriate hospital admissions and consequently hospital deaths. For patients with metastatic lung cancer, treatment could be aimed at life extension or quality of life without any prospect of cure. However, many patients receiving chemotherapy for incurable cancers may not understand that the treatment is unlikely to be curative, which could compromise their ability to make treatment decisions in line with their treatment goals. In the last few decades, patients' satisfaction has become an important endpoint in the assessment of quality of care. It is important for patients with metastatic lung cancer that their expectations are being met for the treatment they receive. Communication of oncologists is therefore of fundamental importance in the treatment decision process. It is known that oncologists may use difficult language to discuss prognosis and treatment options. Also, cancer has a large impact on relatives. As patients and their relatives go along the different phases of the treatment trajectory together, relatives' evaluation on the treatment is also important and may differ from the patients'.

Therefore this thesis aims to study:

- The percentage of metastatic lung cancer patients who received chemotherapy or TKIs in the last month of life in the Netherlands.
- The percentage of metastatic lung cancer patients who died inside the hospital and whether hospital death is associated with receiving systemic treatment in the last month of life.
- The type and the feasibility of treatment goals that patients and their oncologists have when starting systemic treatment.
- To what extent the patients' and their oncologists' treatment goals are achieved after systemic treatment and whether this differed between types of therapy. In addition, whether it was their right decision to start treatment in hindsight.
- The perspective of the relatives in hindsight on the achievement of the patients' treatment goals and whether they are satisfied about the patients' treatment choice.

Chapter 2 presents the percentage of metastatic lung cancer patients who receive chemotherapy or TKIs in the last month of life in the Netherlands. A retrospective patient file

study was conducted in 10 hospitals and included 1322 metastatic lung cancer patients who died between mid-2013 and mid-2015. We found that a substantial percentage of metastatic lung cancer patients received and even started a treatment in their last month of life. In total, 39% of patients received no treatment for metastatic lung cancer, 52% received chemotherapy and 9% received TKIs. A total of 232 patients (18%) received treatment in the last month of life (11% chemotherapy, 7% TKIs). From the patients who received chemotherapy or TKIs, 11% and 12% respectively started this treatment in the last month of life.

Chapter 3 reports on the percentage of metastatic lung cancer patients who died inside the hospital in the Netherlands and whether hospital death is associated with receiving systemic treatment in the last month of life. These results were retrieved from the retrospective patient file study described in **chapter 2** and showed that 18% of patients died during a hospital admission. This percentage was higher for patients who received chemotherapy (42%) or TKIs (25%) in the last month of life. Furthermore, the results showed that patients younger than 60 years of age, patients who received chemotherapy in the last month of life and patients in whom TKIs were started in the last month of life were more likely to die inside the hospital.

Chapter 4 focusses on the treatment goals patients and oncologists have when starting a systemic treatment, what the concordance of patients and oncologist is between these goals and how feasible they think these goals are. The results were based on a longitudinal questionnaire study. For this study 266 patients and their prescribing oncologists filled out a questionnaire about their treatment goals and their estimated feasibility of these goals immediately after the treatment was decided. Patients and oncologists reported 'quality of life' (45%; 72%), 'life prolongation' (45%; 55%), 'decrease in tumour size' (39%; 66%) and 'cure' (19%; 2%) as treatment goals. Additionally, semi-structured interviews were performed in order to better understand patients' and oncologists' treatment goals and thoughts on feasibility. These interviews showed that the goal 'cure' appeared to be often as motivation to stay alive. Concordances between patients' and oncologists' treatment goals were low (ranging from 24% to 33%). Patients had slightly higher feasibility scores than oncologists (6.8 vs 5.8 on a 10-point scale) and we showed that educational level, age, religious views and performance status of patients were associated with treatment goals.

Chapter 5 describes to what extent patients' and oncologists' treatment goals were achieved after systemic treatment and whether it was the right decision to start treatment in hindsight. For this study a part of the participants described in chapter 4 participated: 146 metastatic lung cancer patients and 23 oncologists for 223 patients, wo filled out a questionnaire after the treatment. The exact goal that the respondent had written down in the first questionnaire was copied: for each of these goals it was asked to what extent the goal was achieved and if it was the right decision to start this treatment. This data showed that according to patients and oncologists, treatment goals were achieved in 30% and 37% for 'quality of life', 49%

and 41% for 'life prolongation', 26% and 44% for 'decrease in tumour size' and 44% and 0% for 'cure' respectively. Most patients and oncologists, in hindsight, felt they had made the right decision to start treatment, also if they had not achieved their goals (72% and 93% respectively). Additionally, semi-structured interviews were performed in order to better understand patients' and oncologists' achievement of treatment goals and to give further insight in making the right decision to start treatment. We found that making the right decision to start treatment was related to the feeling that they had to do 'something'.

Chapter 6 elaborates on the perspective of relatives in hindsight on the achievement of patients' treatment goals and whether they are satisfied about the patients' treatment choice. Structured telephonic interviews were conducted with 118 relatives of patients described in chapter 4, at least 6 weeks after the patient died. During the interview relatives were asked to what extent they perceived the treatment goal(s) of the patient as achieved and if they were satisfied with the patients' choice for starting a systemic treatment. Relatives reported the goals 'quality of life', 'decrease tumour size' and 'life prolongation' as achieved in 21%, 37% and 41% respectively. The majority of the relatives (78%) was satisfied with the choice to start a treatment; even when none of the goals were achieved, 70% of the relatives was satisfied. Most often relatives were positive about the patients' treatment decision because they felt that the patient had tried everything to fight the disease and they wanted to support the patient's choice.

Chapter 7, the **General Discussion**, starts off with methodological considerations of the research presented in this thesis. **Strengths** of the studies include the high number of patients and a representative sample of the population. The **limitations** include the lack of report on the preferred place of death for the retrospective patient file study, the selective group of patients being mostly treated in an academic hospital and the dichotomization of the feasibility and achieved score from a scale from 0 to 10 into yes and no for the prospective questionnaire study. Next, the general discussion provides a description of the **main findings** from each chapter in relation to previous research and reflect on treatment, place of death and preferred and achieved treatment goals of metastatic lung cancer patients. Also views of oncologists and relatives on treatment goals and treatment decision are discussed. In the closing part of the chapter, some **recommendations for clinical practice and future research** are described. These include the need for palliative care at the end-of-life, recent research on the percentage of treated metastatic lung cancer patients and further research on the reason and satisfaction on choosing not to treat metastatic lung cancer according to patients and oncologists.

Samenvatting

Hoofdstuk 1 introduceert het onderwerp van dit proefschrift: de behandeling van patiënten met uitgezaaide longkanker in de laatste fase van hun leven. Longkanker is wereldwijd een van de meest gediagnosticeerde kankers. Systemische behandelingen zoals chemotherapie, immunotherapie en doelgerichte therapie met Tyrosine Kinase Inhibitors (TKIs) hebben als doel de symptomen te verminderen en de ziekte onder controle te brengen. Deze kunnen echter ook bijwerkingen veroorzaken en de kwaliteit van leven verminderen. Het behandelen van uitgezaaide longkanker komt steeds meer voor en wordt vaak 'agressieve zorg' genoemd. Dit omdat meerdere onderzoeken hebben laten zien dat behandelingen in de laatste levensfase van patiënten vaak de oorzaak zijn van belastende en ongewenste ziekenhuisopnames, die uiteindelijk kunnen leiden tot overlijden in het ziekenhuis. De behandeling van patiënten met uitgezaaide longkanker waar genezing geen optie meer is, kan gericht zijn op levensverlenging of kwaliteit van leven. Helaas begrijpen veel patiënten die ongeneeslijk ziek zijn en toch een behandeling krijgen, niet goed dat deze behandeling de kanker niet meer kan genezen. In dat geval kan het zijn dat hun behandeldoelen niet overeenkomen met de keuze van hun behandeling. Tevredenheid met de gekozen behandeling is in de afgelopen jaren steeds belangrijker geworden in de kwaliteit van zorg. Het is van belang dat de verwachtingen van patiënten met uitgezaaide longkanker overeenkomen met de mogelijke behandelresultaten. Bij de keuze voor een behandeling, is communicatie tussen patiënt en arts uitermate wezenlijk. Een bekend probleem is dat artsen moeilijke termen kunnen gebruiken wanneer zij de prognose en behandelopties bespreken. Een ander aandachtspunt is dat kanker ook van grote invloed is op de naasten. Bij het doorlopen van een behandeltraject is de ervaring van de naasten over dit traject ook belangrijk en mogelijk kan deze afwijken van die van de patiënt.

In dit proefschrift worden de volgende zaken onderzocht:

- Het percentage patiënten in Nederland met uitgezaaide longkanker die een systemische behandeling krijgt in de laatste levensmaand.
- Het percentage patiënten met uitgezaaide longkanker die in het ziekenhuis overlijdt en in hoeverre dit gepaard ging met een behandeling in de laatste levensmaand.
- Welke behandeldoelen patiënten en artsen hebben wanneer zij starten met een systemische behandeling voor uitgezaaide longkanker, hoe vaak deze doelen overeenkomen en hoe haalbaar deze doelen worden geacht.
- In hoeverre de behandeldoelen die patiënten en artsen hebben, behaald zijn na behandeling van uitgezaaide longkanker en of deze behandeling achteraf gezien een goede keuze was volgens hen.
- De mening van de naasten over het behalen van de behandeldoelen van de patiënt en in hoeverre zij tevreden zijn over de behandelkeuze van de patiënt.

Hoofdstuk 2 geeft inzicht in het percentage patiënten met uitgezaaide longkanker die nog een behandeling met chemotherapie of doelgerichte therapie krijgen in de laatste levensmaand in Nederland. Hiervoor was een retrospectief dossieronderzoek opgezet in 10 ziekenhuizen. In dit onderzoek zijn de gegevens van 1322 patiënten opgenomen met de diagnose uitgezaaide longkanker die overleden waren tussen medio 2013 en medio 2015. We zagen dat een groot deel van de patiënten met uitgezaaide longkanker toch nog een systemische behandeling kreeg; een deel startte zelfs nog in de laatste maand van hun leven met een behandeling. In totaal kreeg 39% van de patiënten geen behandeling voor uitgezaaide longkanker, 52% kreeg chemotherapie en 9% kreeg doelgerichte therapie. Hiervan kregen 232 patiënten (18%) de behandeling in hun laatste levensmaand, 11% chemotherapie en 7% doelgerichte therapie. Van de patiënten die chemotherapie en doelgerichte therapie ontvingen, startten respectievelijk 11% en 12% deze behandeling in de laatste maand van hun leven.

Hoofdstuk 3 rapporteert over het percentage patiënten met uitgezaaide longkanker in Nederland dat in het ziekenhuis overlijdt. Tevens is onderzocht of deze plaats van overlijden geassocieerd is met het ontvangen van een systemische behandeling in de laatste levensmaand. Deze resultaten komen uit het retrospectieve dossieronderzoek beschreven in **hoofdstuk 2**. Het blijkt dat 18% van de patiënten overlijdt in het ziekenhuis. Dit percentage was hoger voor patiënten die chemotherapie (42%) of doelgerichte therapie (25%) ontvingen in hun laatste levensmaand. Ook blijkt dat patiënten die jonger zijn dan 60 jaar, patiënten die chemotherapie in de laatste levensmaand ontvingen en patiënten waarbij doelgerichte therapie in de laatste levensmaand werd gestart, een grotere kans op overlijden hadden.

Hoofdstuk 4 toont de behandeldoelen die patiënten en artsen hebben wanneer zij starten met een systemische behandeling voor uitgezaaide longkanker. Daarbij is geanalyseerd hoe vaak deze doelen overeenkomen en hoe haalbaar zij deze doelen achtten. Deze resultaten zijn gebaseerd op een longitudinaal onderzoek. Voor dit onderzoek vulden 266 patiënten en hun artsen direct na het starten van de behandeling een vragenlijst in over hun behandeldoelen en de haalbaarheid. Patiënten en artsen gaven ‘kwaliteit van leven’ (45%; 72%), ‘langer leven’ (45%; 55%), ‘verminderen van de tumor’ (39%; 66%) en ‘genezing’ (19%; 2%) aan als behandeldoelen. Daarnaast waren er semigestructureerd interviews uitgevoerd om meer inzicht te krijgen in de behandeldoelen en haalbaarheid van patiënten en artsen. Het blijkt dat het doel ‘genezing’ vooral een motivatie was om in leven te blijven. Overeenkomsten tussen de doelen van patiënten en die van de artsen waren gering, tussen de 24% en 33% per doel. Patiënten hadden over het algemeen een hogere haalbaarheidsscore ten opzichte van artsen (6.8 t.o.v. 5.8 op een 10 punt-schaal). We lieten tevens zien dat opleidingsniveau, leeftijd, religie en functionele status van patiënten geassocieerd werden met bepaalde behandeldoelen.

Hoofdstuk 5 beschrijft in hoeverre de behandeldoelen van patiënten en artsen behaald waren na een systemische behandeling voor uitgezaaide longkanker en in hoeverre die behandeling achteraf gezien een goede beslissing was. In dit onderzoek heeft een deel van de populatie uit **hoofdstuk 4** deelgenomen: 146 patiënten met uitgezaaide longkanker en 23 artsen voor 223 patiënten, die na de behandeling een vragenlijst ingevuld hadden. Van ieders behandeldoel dat de patiënt en arts vooraf hadden opgeschreven werd gevraagd in hoeverre dit behaald was en of het achteraf gezien de juiste behandelkeuze was. Volgens patiënten en artsen, zijn de behandeldoelen behaald in respectievelijk 30% en 37% voor 'kwaliteit van leven', in 49% en 41% voor 'langer leven', in 26% en 44% voor 'verminderen van de tumor' en in 44% en 0% voor 'genezing'. De meeste patiënten en artsen vonden achteraf gezien in 72% en 93% dat ze een juiste behandelkeuze hebben gemaakt. Dit zelfs wanneer de behandeldoelen niet werden behaald. Ook zijn er semigestructureerde interviews uitgevoerd om meer inzicht te krijgen in het behalen van de behandeldoelen en waarom het een goede keuze was om te starten met de behandeling. Hieruit blijkt dat een goede keuze voor de behandeling te maken heeft met het gevoel van 'iets doen' tegen de ziekte.

Hoofdstuk 6 presenteert de mening van de nabestaanden over het behalen van de behandeldoelen van de patiënt en in hoeverre zij tevreden zijn over de behandelkeuze van de patiënt. Gestructureerde, telefonische interviews zijn uitgevoerd met 118 nabestaanden van de populatie uit **hoofdstuk 4**, minimaal 6 weken nadat de patiënt overleden was. Daarbij is hen gevraagd of de behandeldoelen van de patiënt behaald zijn en of zij tevreden zijn met de behandelkeuze van de patiënt. Nabestaanden gaven aan dat de doelen 'kwaliteit van leven', 'verminderen van de tumor' en 'langer leven' respectievelijk behaald zijn in 21%, 37% en 41%. De meerderheid (78%) is tevreden over de behandelkeuze. Zelfs wanneer volgens hen geen enkel behandeldoel behaald was, was alsnog 70% tevreden. Nabestaanden zijn meestal positief over de beslissing om te starten met een behandeling omdat zij van mening zijn dat de patiënt alles heeft geprobeerd om de ziekte te bevechten en omdat ze deze keuze ondersteunen.

Hoofdstuk 7, de **algemene discussie**, begint met methodologische overwegingen van de onderzoeken uit dit proefschrift. **Sterke punten** van deze onderzoeken zijn de grote aantallen van patiënten en een representatieve groep uit de populatie. **Zwakke punten** zijn dat in het retrospectieve dossieronderzoek de gewenste plaats van overlijden niet bekend was en dat in het longitudinale vragenlijstenonderzoek vooral patiënten uit een academisch centrum deel hadden genomen. Daarna beschrijft de algemene discussie de hoofdbevindingen van ieder hoofdstuk in relatie tot de bekende literatuur en belicht het de behandeling, plaats van overlijden en beoogde en behaalde behandeldoelen van patiënten met uitgezaaide longkanker, tezamen met het perspectief van de artsen en nabestaanden over de behandeldoelen en de tevredenheid met de keuze van behandelen. In het laatste deel van het hoofdstuk worden enkele **aanbevelingen voor de praktijk en toekomstig onderzoek** beschreven. Deze bevatten

de noodzaak van palliatieve zorg in de laatste levensfase, recenter onderzoek naar het percentage patiënten dat behandeld wordt voor uitgezaaide longkanker en de aanbeveling voor meer onderzoek naar de reden en tevredenheid van het niet behandelen van uitgezaaide longkanker volgens patiënten en artsen.

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In dit dankwoord wil ik graag verschillende mensen bedanken die belangrijk zijn geweest gedurende de tijd dat ik aan dit proefschrift heb gewerkt.

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Ella en **Nynke**, mijn geweldige paranimfen. **Nynke**, wij hebben elkaar leren kennen bij de Ronde Tafel in Emmeloord. Jij als huisarts en ik als promovenda hadden direct een klik op werkgebied. Maar later bleek dat we het daarnaast ook heel goed samen konden vinden met onze gedeelde interesses. Hardlopen, bakken, filmavondjes met wijn en kaas, we hadden elke week wel iets op de planning. Ik miste je ook erg toen ik naar Amsterdam verhuisde, maar

gelukkig zien we elkaar nog regelmatig. Ik ben erg blij dat je op deze dag naast mij staat, met die prachtige mooie jurk, hé Lex ;). Je bent lief, geïnteresseerd, oprecht en lekker nuchter. Dat laatste heb ik soms echt wel een beetje van je nodig, als ik me weer ergens druk om maak. Ik hoop dat we nog velen jaren goeie vriendinnen zullen blijven en dat we snel met **Lex**, **Koen** en **Tijs** op wintersport mogen gaan.
Ella, mijn grote voorbeeld, rots in de branding en lieve vriendin. Wij hebben elkaar leren kennen bij het VUmc. Jij als coördinator van het stafsecretariaat en ik als één van de vele promovendi die haar administratie weer niet op orde had toen ze bij het VUmc kwam werken. Als snel kwamen we samen in de redactie van het personeelsblad van de afdeling Longziekten. Dan gingen we wel eens met z'n allen uit eten en we raakten steeds vaker samen aan de praat. Het klikte gewoon goed denk ik :). Meer avondjes volgden waarbij de wijn en kaasjes altijd van perfecte kwaliteit zijn. In april 2020 liep mijn contract af en ging jij met pensioen. Het lijkt mij niets mooiers om de jaren VUmc samen met jou af te sluiten. Je begrijpt het doel van mijn onderzoek en de ernst in deze patiëntenpopulatie als geen ander. Jouw gevoel voor taal heeft dit proefschrift wel degelijk verbeterd en als een van de weinige mensen heb jij (en Donné deels) het helemaal gelezen. Ik tref het maar Ella, mijn lieve vriendin, om jou naast mij te hebben tijdens de verdediging en deze mooie dag. Ik zou je nergens anders willen hebben dan aan mijn zijde. **Donné**, **Anna** en **Elza**, fijn dat ik jullie heb leren kennen!

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Lieve **Theo**. Als iemand mij met hart en ziel heeft bijgestaan in mijn promotieonderzoek ben jij het wel. Vanaf het begin af aan hebben we elke week samen hardgelopen (zelfs de halve marathon van Amstelveen). Even m'n hoofd leegmaken, even kletsen over werk maar vooral over alle andere dingen in ons leven. Zelfs na mijn verhuizing naar Alkmaar zijn we elkaar blijven zien en rennen, wandelen of drinken we koffie samen. Ik hoop dat ik gelijk heb als ik zeg dat wel elkaar niet snel uit het oog zullen verliezen. Ik jou in ieder geval niet.

Rob, je bent me er een. Zo attent en behulpzaam. We hebben elkaar met de PhD training leren kennen en ik hoop dat we elkaar zullen blijven zien.

Lieve (tante) **Julia**, je bent met recht mijn gekste en grappigste vriendin. Mede-promovenda, mede-levensgenieter, goede kok en altijd up to date met de laatste mode. Ik heb je leren kennen op een kerstborrel van Jong Amsterdam UMC (zonnebrand bruin!) en sindsdien waren we onafscheidelijk. Wat mis ik de feestjes met jou! Gelukkig borrelen en eten we thuis vrolijk

verder. Het ping-pong feest met jullie **Ires** en **Tjarda** gaat voor mij de boeken in als laatste Jong Amsterdam UMC feestje. Bedankt voor alle gezelligheid dames! En wie kon die feestjes beter organiseren dan jij, **Thomas**. Ook met jou heb ik veel geborreld en theetjes gedronken, maar ook geboulderd en we waren zelfs naar La Roux. Je bent zo'n ambitieus, warm en grappig persoon, ik ben blij met jou als vriend!

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Ik heb meerdere cursussen richting carrière en persoonlijke ontwikkeling gevolgd en deze vraag kwam hier vaak naar voren: wat is voor jou het allerbelangrijkste in je leven? Voor mij is dat familie. Lieve familie, jullie zijn mij zoveel waard. Bij jullie kan ik mezelf zijn, hebben we het gezellig, doen we leuke dingen en kletsen we onder andere ook over mijn onderzoek. **Wim** en **Joke**, jullie zijn slim en betrokken, altijd geïnteresseerd en ik ambieer een levensstijl zoals die van jullie; ambitieus, sportief en sociaal actief. **Fenna**, **Fiene**, **Didde**, **Ole** en **Jibbe**, bij jullie is het altijd gezellig. Wijntjes met jou Fen, en bios, logeerpartijtjes, schilderen, bakken en wiskunde sommen maken met de kids. Ik geniet altijd van jullie. **Giel**, **Celine**, **Faye**, **Gieltje**, **Benn** en **Youp**, bij jullie ben ik kind aan huis. Giel's uitstekende kookkunsten, oneindig veel avondjes kletsen en wijn drinken met jou Celine, de leuke dagjes Amsterdam met Faye, karten

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Lieve Wessel, wil je samen met mij en ons kindje op komst, de wereld blijven ontdekken?

About the author

Adinda Mieras was born on April 2nd 1990 in Hoorn, the Netherlands. In 2009 she finished secondary school. From 2009-2013 she obtained her bachelor of Biology and Medical Laboratory research at the Hogeschool van Hall Larenstein in Leeuwarden. After having her bachelor's degree she followed a pre-master program Human Movement Sciences at the Rijksuniversiteit Groningen in 2013. From 2014-2016 she followed the Master Human Movement Sciences and specialized herself into Motor Function and Cognition in Healthy Ageing. She performed research on the dissociation between behaviour and motor cortical excitability before and during a wrist flexion and extension task in young and old adults. After finishing her masters she began to work as a Ph.D. candidate at the pulmonary department and the end-of-life care research group at the Amsterdam UMC, location VU medical centre from 2016-2020. From 2017-2019 she completed a post-graduate Master of Science in Epidemiology, including specialized courses concerning methodology and quantitative analysis. While finishing her thesis, the COVID-19 pandemic emerges and Adinda found herself coordinating a randomized, double-blind, placebo controlled clinical trial in patients with severe COVID-19 at the pulmonary department of the Noordwest Ziekenhuisgroep in Alkmaar. In June 2020 she started working as a post-doc at the Netherlands Cancer Institute in Amsterdam, with the main function of setting up and coordinating a biobank to facilitate research on genetic susceptibility and markers for late effect of treatment in Hodgkin Lymphoma survivors. Adinda lives in Amsterdam together with her boyfriend Wessel and they are currently expecting their first child. In her spare time she does volunteer work and enjoys sports (ice-speed skating, swimming, cycling, running, hiking and mountain climbing), playing piano, reading and she follows a painting course.

List of Publications

Oral imatinib to prevent pulmonary vascular leak in Covid-19 – a randomized, double-blind, placebo controlled, clinical trial in patients with severe Covid-19 (COUNTER COVID study). J. Aman, E. Duijvelaar, L. Botros, A. Kianzad, J.R. Schippers, P.J. Smeele, S. Azhang, I.H. Bartelink, P.M. Bet, W. Boersma, P.I. Bonta, K.A.T. Boomars, L.D.J. Bos, J.J.M.H van Bragt, G.J. Braunstahl, L.R. Celant, K.A.B. Eger, J.J.M. Geelhoed, Y.L.E. van Glabbeek, H.P. Grotjohan, L.A. Hagens, C.M. Happe, L.M.A. Heunks, M. van den Heuvel, W. Hoefsloot, R.J.A. Hoek, R. Hoekstra, H.M.A. Hofstee, N.P. Juffermans, A. Lammers, R. Kos, E.M. Kemper, P.W.A. Kunst, I. van der Lee, E.L. van der Lee, P.F.M. Mau Asam, A.H. Maitland-Van der Zee, A. Mieras, E.J. Nossent, M.J. Overbeek, L.M.A. Oswald, N. Paternotte, C. Pamplona, N. Pronk, M.A. de Raaf, E.M. Slob, A. Serpa Neto, M.J. Schultz, M.R. Smit, F. Smeenk, A.J. Smits, J.E. Stalenhoef, P.R. Tuinman, A.L.E.M. Vanhove, J. Wessels, A. Vonk Noordegraaf, F.S. Handoko-de Man, H.J. Bogaard. *Submitted 2021.*

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Dissociation between behavior and motor cortical excitability before and during ballistic wrist flexion and extension in young and old adults. Tibor Hortobagyi, Adinda Mieras, John Rothwell, Miguel Fernandez del Olmo. *PLOS ONE (2017).*


Art-mella